

Exhibit B

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

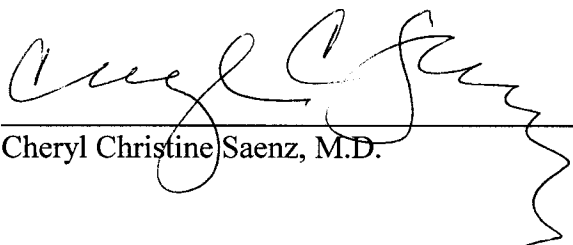
**IN RE: JOHNSON & JOHNSON TALCUM
POWDER PRODUCTS MARKETING, SALES
PRACTICES AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**EXPERT REPORT OF CHERYL CHRISTINE SAENZ, MD
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019


Cheryl Christine Saenz, M.D.

Background and Qualifications

My name is Cheryl Christine Saenz, MD and I am a Clinical Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Diego. I have been an attending physician at UC San Diego Health System for over 20 years, since October 1998. My current academic appointment is as a clinical professor of gynecologic oncology, where I serve as an educator, a clinician and a researcher.

As an educator, I am responsible for teaching fellows, residents and medical students about all aspects of gynecologic malignancies, including their epidemiology, risk factors for development, histopathology and pathophysiology, prevention, diagnosis and treatment. All levels of learners actively participate in my clinical practice in the operating room and the clinics, and I serve as the attending supervising physician for the Fellows' Clinic to help train the next generation of gynecologic oncologists.

As a clinician, I perform surgical procedures and prescribe chemotherapy and immunotherapy for my patients with reproductive cancers. I have a robust clinical practice, as on average, I care for 40-50 patients per week in the clinics and operate on 4-5 patients per week. My patients are typically women with known gynecologic malignancies or known to be at significant risk of developing a gynecologic malignancy. I develop long-term relationships with most of my patients and their families, as they stay in follow-up with me from the time of diagnosis until they are either cured, or unfortunately succumb to their disease. In patients whose cancer recurs, this usually happens within five years of diagnosis, and for those whose cancers do not recur, we consider them to be cured at the five-year landmark. At this juncture, we usually transition our patients into a Survivorship program. To help ensure that the gynecologic cancer care we deliver at UC San Diego Health System is up to date and consistent with national guidelines, we maintain a bi-weekly multi-disciplinary Treatment Planning Conference for the gynecologic oncology service, and I have served as the medical director of that conference for the past 15 years. Additionally, I served as the Chair of the Cancer Committee at the Moores UCSD Cancer Center for a tenure of twelve years. Under my direction, our cancer care program consistently achieved accreditation from the Commission on Cancer, a program of the American College of Surgeons, and was recognized for providing comprehensive, high-quality and multidisciplinary patient-centered care. This accreditation was an integral component in the Moores UCSD Cancer Center selectively achieving National Cancer Institute (NCI)-designated "Comprehensive Cancer Center" status. Only 49 such programs exist in the United States.

I am an active researcher, participating in cooperative group trials, studies investigating new therapeutic options for cancer treatment, and I serve as the primary investigator in investigator-initiated studies at the Moores UCSD Cancer Center. As a member of the Gynecologic Oncology Group, the largest cooperative trials research group investigating women's cancers, I served as a member of the cervix and vulvar cancer committee and

as a member of the vaccine subcommittee. One of my most active areas of investigator-initiated research is in the early detection of ovarian cancer. Through collaboration with colleagues in the fields of genomics and nanoengineering, we are in the process of developing screening tests that may be able to detect isoforms of mRNA unique to ovarian cancer. These isoforms can be found in cells collected on a Pap smear of the cervix or peripherally in a sample of the patient's blood, long before the ovarian cancer becomes clinically significant. As a result of this work, I have been named the Medical Director of the Strauss Family Center for the Early Detection of Ovarian Cancer. Our hope is that with continued research, we will be able to use our findings to apply our screening test in a manner that will lead to earlier detection of this cancer and improvements in overall prognosis. My research in ovarian, cervical and endometrial cancers has been extensively published in such journals as *PNAS*, *Nature Communications*, *Gynecologic Oncology*, *Cancer Research* and *PLoS Biology*.

I attended Cornell University and graduated with a BA in Biopsychology in 1985. I completed my medical school training at the University of California, Irvine and then enrolled in a four-year residency program in Reproductive Medicine at the University of California, San Diego. During this time, I was awarded a Galloway Fellowship at Memorial Sloan Kettering Cancer Center. At the completion of my residency, I was accepted into the board-eligible fellowship in Gynecologic Oncology at Memorial Sloan Kettering Cancer Center and completed my training in 1998. I was initially boarded in Obstetrics and Gynecology in 1999 and in Gynecologic Oncology in 2001, by the American Board of Obstetrics and Gynecology. I have maintained my certification in both fields, with my most recent recertification being in 2018.

I am a full member of the Society of Gynecologic Oncology and the American Society of Clinical Oncology, a Fellow of the American College of Surgeons and the American Congress of Obstetrics and Gynecology. I received a National Institutes of Health Women's Reproductive Health Research Scholars Fellowship from 2002-2007 and a NCI Clinical Investigator Team Leadership Award from 2010-2012. This award recognizes outstanding investigators whose participation and activities promote successful clinical trial research programs. I served on the Board of Directors of the Foundation for Women's Cancer from 2007-2013 and served as the Chair of that Foundation's Education Committee from 2013-2016. I have been retained as a content expert on bills presented to the California state legislature on ovarian cancer screening and health care coverage for gynecologic cancer screening tests. I have served as course director for many ovarian cancer survivors' courses (supported by the Foundation for Women's Cancer and the Society of Gynecologic Oncology) as well as the BeWise (Better Education for Women in Science and Engineering) Saturday Academy, a philanthropically-funded program in San Diego County, which mentors young women in high school to encourage them to pursue careers in science and medicine. My opinions in this report are based upon my education, experience and expertise in the field of Gynecologic Oncology. I also base my opinions on my review of the peer-reviewed published scientific literature. All opinions are stated to a reasonable degree

of medical certainty. I am being compensated at a rate of \$750 per hour for my work on this matter and \$1200 per hour for any time spent testifying at deposition or in court.

Ovarian Cancer – Overview

In the United States, ovarian cancer ranks 5th in cancer deaths in women and causes more cancer deaths than all of the other gynecologic malignancies combined. It is estimated that 22,240 women were diagnosed with ovarian cancer and 14,070 women died from this disease in 2018 (57). Over the course of her lifetime, a woman's risk of developing ovarian cancer continues to increase, with an overall estimate of 1.3%. The mean age of diagnosis is 63 years old. The most common type of ovarian cancer originates from the epithelial cells that occur on the surface of the ovary. Malignant epithelial cells have distinct histologic subtypes, and these include serous (the most common at ~70% and includes cancers that originate in the Fallopian tube or from the lining of the abdominal cavity, called primary peritoneal cancer), mucinous, endometrioid and clear cell carcinoma. Each of these histologic subtypes has a distinct molecular profile, chemosensitivity pattern and can vary in risk factors for development.

In general, factors that are well established as increasing a woman's risk of developing ovarian cancer include age, genetics, family history and personal history of cancer, reproductive history (including early menarche and late menopause). Other risk factors have been associated with an increased risk of developing specific histologic subtypes of ovarian cancer. These include endometriosis (associated with endometrioid and clear cell carcinoma), tobacco use (associated with mucinous carcinoma) and obesity (associated with borderline, endometrioid, clear cell and mucinous carcinomas). Additionally, there are other factors that appear to decrease a woman's risk of developing ovarian cancer, and these include use of oral contraceptive agents for at least five contiguous years, tubal ligation, the age at which a woman first gives birth as well as the number of births, breastfeeding for on average six months with each child and surgical removal of the ovaries and tubes. Some authors refer to these factors as "protective," but I do not believe that terminology is appropriate, as these factors cannot prevent the disease, they are simply associated with a reduced risk of development.

Prognosis for patients with epithelial ovarian cancer is heavily dependent upon stage at diagnosis, and unfortunately the majority of women are diagnosed with advanced stage disease, which in most cases is incurable. Much research has focused on trying to identify effective screening tests for ovarian cancer, as this could improve prognosis. This research has been challenging, however, as we really do not know what ovarian cancer looks like as it is developing, unlike cancers of the colon, breast and cervix. Several hypotheses exist that attempt to explain how each of the established risk factors could ultimately be involved in the causation of ovarian cancer; however, each of these is simply still a hypothesis. The epidemiologic literature can demonstrate associations,

but it cannot assign causation, and the cancer biology literature lacks consistent data demonstrating how ovarian cancer develops.

Established Risk Factors for the Development of Ovarian Cancer

Age

Age itself is an independent risk factor for the development of ovarian cancer. The majority of epithelial ovarian cancers are diagnosed in women 55-64 years old. As a woman ages, her risk of ovarian cancer continues to increase, peaking in the late 70s.

Genetics

One of the most well established risk factors for the development of epithelial ovarian cancer is the inheritance of a gene that is mutated in a manner that can predispose a woman to the development of ovarian cancer. Approximately 10% of women diagnosed with ovarian cancer are found to have inherited such a deleterious mutation, but when that analysis is restricted to women whose ovarian cancer is of serous histology, the rate increases to approximately 30%. The majority (~70%) of these mutations are found in either BRCA1 or BRCA2. However, mutations can also be found in a cluster of genes that are often referred to as the “BRCA-ness” genes, and these account for ~29% of the inherited ovarian cancers (85). To date, roughly 16 different genes have been identified in this cluster, but new genes are being identified and added to testing panels every year. In the mid-1990s, we only tested for two genes (BRCA 1 and 2); by contrast, the expanded panel testing currently available through many commercial labs, examines more than 25 different genes. HNPCC, or Lynch syndrome, genes are responsible for the remaining ~1% of the inherited ovarian cancers. It is presently thought that there are still genes yet to be identified that will fall into the “BRCA-ness” category that will ultimately reveal that closer to 20-25% of all ovarian cancers are actually linked to inheritance of a loss-of-function mutation. Importantly, many of the women found to have inherited a deleterious mutation have no prior family history of breast or ovarian cancer (85). And as reported by Eng (2018), when the inherited mutation is being transmitted through the paternal lineage, the cancer risk may appear to “skip” generations, particularly if the mutation has an X-linked pattern of inheritance (18). The lifetime risk of developing ovarian cancer for a woman who inherited a deleterious mutation varies, as it is dependent upon the individual mutation, but the risk for an inherited mutation in BRCA1 is estimated to be 40-53% and for BRCA2 20-30% (65). This equates to roughly a 20-50 times higher lifetime risk of developing ovarian cancer than a woman who does not carry such a mutation.

Family and Personal Cancer History

Women with a family history of ovarian cancer (even in the face of negative or absent genetic testing) are at an increased risk of developing ovarian cancer themselves. The lifetime risk of a woman who has a first-degree relative with ovarian cancer is 5%, which is three times higher than an average woman’s risk. The risk is even higher if the

affected relative was <50 years old at the time of diagnosis (86). Additionally, a family history of breast cancer, colon cancer, rectal cancer and uterine cancer increases a woman's risk of developing ovarian cancer over the background population risk. Any woman who herself has been afflicted by cancer is at an increased risk for developing ovarian cancer. In particular, a personal history of breast cancer, uterine cancer, cervical cancer, thyroid cancer, melanoma, colon or rectal cancer increases the risk of developing ovarian cancer (32).

Reproductive History, Early Menarche and Late Menopause

It is well established that women who are nulliparous have an increased risk of developing ovarian cancer. Women who have ever given birth appear to have a reduced risk, with each subsequent pregnancy reducing the risk further by 10-20% (87). The age at which a woman has her first child also appears to influence risk as women who have their first child later in life (>35 years old) appear to have less reduction in risk than those who have their children earlier. Additionally, any woman who has been diagnosed with infertility is at an increased risk of ovarian cancer, and this risk remains whether or not fertility agents were used (which incidentally are not known to be a risk factor) (83).

Consistently over the years, early age at menarche and late age at menopause have been associated with an increased risk of developing ovarian cancer. This finding has been interpreted to mean that the higher the number of ovulatory events that occur in a woman's lifetime, the higher her risk of developing ovarian cancer. This has led to the proposal of the incessant ovulation hypothesis of ovarian cancer development. Fathalla first published this hypothesis in 1971, and the theory is that the disruption of the surface epithelium of the ovary that occurs with each ovulatory event can ultimately lead to malignant transformation (19). The data for the influence of age at menarche seems variable, but the age of menopause data seems more consistent, with each five-year increase in the age of menopause increasing the risk of ovarian cancer by ~6% (87). Nonetheless, support for the incessant ovulation hypothesis is still lacking, as studies on ovulatory suppression do not entirely account for the magnitude in risk reduction seen with these interventions (e.g., breastfeeding, pregnancy and oral contraceptives) (89).

Postmenopausal Hormone Replacement Therapy

Use of postmenopausal hormone replacement therapy has waxed and waned over the years as various studies have reported on the health benefits vs. risks associated with the use of this therapy. Despite this, the use of postmenopausal hormones has consistently been associated with an increased risk of developing ovarian cancer (9). Estimates are that the risk increases in the range of 20-40% for five years or more of use, and the risk continues for at least five years, even after the woman stops using the hormone replacement therapy.

Histologic Specific Risk Factors

Endometriosis

Endometriosis has been found to increase a woman's risk of developing ovarian cancer by 2-3 fold. The risk seems particularly strong for women who are found to have endometrioid or clear cell histologies of epithelial ovarian cancer, with endometrioid adenocarcinomas accounting for 69% and clear cell carcinomas accounting for 13.5% of the ovarian malignancies associated with endometriosis (22). These percentages are far higher than the percentages of these histologies found in ovarian cancers not associated with endometriosis (10-20% and 3-10%, respectively). The additional finding of cytologic atypia in implants of endometriosis (akin to the precancerous hyperplasia with atypia that precedes the development of endometrial cancer) supports the hypothesis that endometrioid and clear cell carcinomas undergo a different process of malignant transformation than do serous carcinomas (71). Other "inflammatory" conditions, such as polycystic ovarian syndrome and pelvic inflammatory disease, have not consistently been found to alter a woman's risk of ovarian cancer (see below).

Tobacco

For a multitude of health reasons, use of tobacco is a poor choice. For the purposes of this review, however, there is a clear association between use of tobacco and the development of the mucinous histologic subtype of ovarian cancer (86). Much like any environmental exposure that is found to be carcinogenic, the risk of developing ovarian cancer increases with longer durations of smoking, demonstrating an expected dose-response curve (42).

Obesity

Not all studies have consistently demonstrated a relationship between obesity and ovarian cancer. In the studies that have demonstrated such an association, obesity seems to not only increase a woman's risk of developing ovarian cancer, but also portend a worse prognosis, with an increase in the risk of mortality (50). Most studies that have examined the relationship between obesity and ovarian cancer have identified a mildly increased risk in the range of 5-30%, and this risk is more commonly associated with borderline, mucinous, endometrioid and clear cell carcinomas (60).

Factors Associated with a Reduction in Risk

Oral Contraceptives

There is a clear association with the use of combined oral contraceptives and a reduction in the risk of developing ovarian cancer. This holds true even for women with BRCA 1 and 2 mutations (55). Examination of the published data shows no benefit to "ever-users" (as opposed to "never-users") if the contraceptive was only used for 1-4 years (8). Across many studies, the reduction in risk with five years or more of contiguous use has been shown to be in the range of 20-50% and continues with

increasing duration of use in five-year increments. Additionally, the benefit in risk reduction is maintained for at least 30 years after cessation of the oral contraceptives.

Tubal Ligation and Hysterectomy

Women who have had a tubal ligation appear to benefit from a reduction in their risk of developing ovarian cancer by ~20-30%. The actual mechanism for this association has yet to be elucidated, but seems to reduce the risk of developing endometrioid and clear cell carcinomas more than invasive serous carcinomas (75). This reduction in risk may last up to 30 years after the surgery is performed. The association between having a hysterectomy and the development of ovarian cancer is less clear. Some studies have shown a reduction in risk and others have not (87). This relationship is not as well established as the one demonstrated with tubal ligation.

Breastfeeding

Breastfeeding has been associated with a reduction in the risk of developing ovarian cancer in the range of 20-25%. Some studies have shown that the more individual children a woman breastfeeds and the longer the duration of breastfeeding, the more the risk reduction (49). Other studies have demonstrated that for each child that is breastfed, the observed benefit to the woman seems to plateau at ~6 months of breastfeeding, which is presumably when a woman would begin to ovulate again (44).

Surgical Removal of the Fallopian Tubes and Ovaries

A certain percentage of high-grade serous carcinomas that were previously thought to originate in the ovary are now thought to originate in the Fallopian tube. This is particularly true for women who harbor mutations in one of the genes associated with an increased risk of developing "ovarian" cancer. As such, and given that there is no effective screening for these malignancies, women considered to be at high risk for their development are often advised to have prophylactic surgical removal of these structures once they have completed their childbearing, or between the ages of 35-40 years old. This surgical procedure confers a reduction in risk of developing the disease of ~90%, as the risk of primary peritoneal cancer (a malignancy that develops from the same cell of origin as ovarian cancer) still remains. Because there is presently no effective screening that can detect the development of ovarian or Fallopian tube cancer in its pre-invasive or early stages, the risk-reducing surgery also confers a survival benefit to women at high risk for the development of these diseases (16). In high-risk women who do not have prophylactic surgery and in whom the disease does develop, 75% of them are diagnosed with advanced stages, which are most often incurable (57).

Summary

In summary, there are several well-established risk factors that have been associated with a woman having an increased risk of developing ovarian cancer. The most influential of these are mutations in genes that can be inherited and increase the risk of developing ovarian cancer to as high as 50-60% over the course of a woman's lifetime. Genetic mutations, along with the other risk factors discussed above, are all well and

generally accepted by the medical community, because of the consistency, biologic plausibility and strength of the associations in the published literature. This is evidenced by the publication of these risk factors on the respective websites of many of the most well respected scientific organizations such as the Society of Gynecologic Oncology, the American Congress of Obstetricians and Gynecologists, NCI and the Centers for Disease Control (76,1,56,58,5). Notably, none of these organizations recognizes talc as a risk factor for the development of ovarian cancer.

Genital Application of Talc and the Risk of Ovarian Cancer – Overview

The proposed association between use of talc in the genital area and an increased risk of ovarian cancer was first reported ~35 years ago. Despite many years of research on this topic, the scientific evidence does not support a causal role in the development of ovarian cancer with application of talc to the perineal region. First, the epidemiologic literature on this topic is inconsistent. The majority of the published studies consists of small retrospective case-control studies with inherent selection and recall biases. Many of these studies have internal discrepancies and contradict each other, and none of them is able to demonstrate a consistent dose-response curve. A few cohort studies have been published on this subject, and these studies have enrolled large numbers of women, who were followed prospectively, thus removing selection and recall biases, making the data and outcomes more credible. None of the cohort studies demonstrates a statistically significant association between talc and ovarian cancer. Several meta-analyses and one pooled analysis have also been published (mainly with data pulled from the case-control studies). Some authors have proposed the use of pooled analyses and meta-analyses to group the case-control studies together to give more power to the association, but this logic does not always result in stronger science, as these larger studies are subject to the same design errors and biases of the original studies from which they were combined. By and large, the meta-analyses all show the same modest increase in odds ratio in the range of 1.24-1.4. The primary reason for the consistency across the meta-analyses is very likely the fact that they all used many of the same case-control studies in each of the analyses. Simply put, they all re-churned overlapping data sets. A key component to the hypothesis that perineal application of talc can increase the risk of ovarian cancer is the proposal that the talc can migrate from the perineum to the ovaries. Some have offered that the female genital tract is an “open conduit,” across which any number of substances can freely traverse in any direction. There is not a single study demonstrating such migration from the perineum to the ovaries. In deposition testimony, plaintiffs’ expert Dr. Clarke-Pearson admits that he cannot cite any study, animal or human, that traces externally applied talc up through the reproductive tract to the ovaries (pp. 89-90); nor can he cite a single publication that identifies inflammation anywhere in a woman’s reproductive tract resulting from external talc application to the perineal area (p. 88). This last admission is particularly germane, as plaintiffs’ experts have proposed that the mechanism by which talc reportedly induces ovarian cancer is through the induction of an inflammatory

response. This is pure conjecture, as there is no general acceptance that chronic inflammation causes ovarian cancer and chronic inflammatory processes such as pelvic inflammatory disease have not consistently been shown to be associated with an increased risk of developing ovarian cancer.

Epidemiologic Literature

Case-Control Studies

Plaintiffs' expert, Dr. Smith-Bindman, reports that there are 30 original case-control studies that have been published on the association between the perineal use of talc and the development of ovarian cancer. The term "original" is used somewhat loosely, as some of the studies have either simply republished the exact same data set, adding new "findings" and calling it a new study (30,64), or they have subsumed the data from an earlier publication and then added additional subjects for the later publication, thereby calling it an original study (14,15,63,91,92). Of the 30 studies Dr. Smith-Bindman cites in Table 4 of her report, she claims that one failed to report an odds ratio (although this was clearly documented in the paper) (Pike (2004)), and another failed to report a confidence interval (Shushan (1996)), and she thereby claims the statistical significance of these two studies is impossible to evaluate. Additionally, Dr. Smith-Bindman does not include Cramer (2016) as a case-control study, and instead categorizes it as a pooled analysis (15). The published title of this paper, however, includes the phrase "A retrospective case-control study," so it was included in my analysis as a case-control study, respecting the authors' characterization. When the four case-control studies that had their data subsumed into later publications are eliminated from the analysis, this leaves 26 original case-control studies that are available for analysis as to whether or not perineal use of talc results in an increased risk of developing ovarian cancer. Of these 26 published studies, only 12 of them demonstrated a statistically significant increased risk of developing ovarian cancer with the ever-use of talc in the perineal area as compared to never users. This means that 54%, or more than half, of the original published case-control literature has failed to demonstrate a statistically significant association between talc and ovarian cancer (Table 1). In the studies that did demonstrate a statistically significant association, the typical odds ratio was in the range of 1.3-1.5, which is a modest increase and could still be attributable to random chance, as the strength of the association is weak. None of the studies demonstrated an odds ratio of >2 when looking at never/ever perineal use of talc and ovarian cancer. Dr. Smith-Bindman's analysis of these same studies is listed as Table 4 in her report. She states, "the primary research question that I focused on in my review and that was assessed in all included individual research studies, was whether genital area exposure to talcum powder increases risk of epithelial ovarian cancer." Although she states that Table 4 in her report lists the OR as reported in the individual case-control studies for any genital exposure to talc, a careful check of the data in her table reveals that this is not the case. There are places where she reports an incorrect OR or leaves it out entirely, other places where she misrepresents the CI, and

yet others where she claims the study demonstrated statistical significance between any exposure to talc and an increased risk of developing ovarian cancer, when in fact the findings were not significant. Another example of her incorrect reporting is where she lists in Table 4 that Wu (2009) showed an odds ratio >2 , for any perineal exposure to talc, but that is a misrepresentation of the actual results in that study (91). Wu (2009) did not limit the analysis to just perineal use, and instead included all uses of talc, regardless of site of application, when evaluating frequency and duration of use. Wu (2009) only found a 2.08 odds ratio for women that used talc on any body site, for more than 20 years of use and more than 30 applications per month. When looking at never vs. ever use of talc, limited exclusively to perineal application, this study found an odds ratio of 1.53. Wu (2009) also clearly has methodological problems, as in the analysis the authors reported that family history was not significantly associated with the development of ovarian cancer with an OR of 1.76 (0.89,3.47) (91). In the medical and scientific communities, one of the most well accepted and established facts about ovarian cancer is that having a family member with either ovarian or breast cancer raises an individual woman's risk of developing ovarian cancer at least three times higher than the background population risk (45,77). But the Wu (2009) study – which examined this relationship as an “internal control” – failed to demonstrate a statistically significant association between a family history of breast or ovarian cancer and the development of ovarian cancer (91) (45,77), which destroys the credibility of all the study's findings.

Other case-control studies that report positive associations between talc and ovarian cancer have also suffered from internal inconsistencies. Cramer (2016) reports an OR of 1.33 (CI 1.16,1.52) (15). As discussed more fully below, the authors of this study assert that they demonstrate a dose-response curve with their data, as subjects were found to have an increased risk the more frequently they applied talc perineally. They also report a positive finding for years used; however, the reported odds ratios are actually flat with the OR for < 8 years of exposure being essentially the same as > 35 years of exposure (1.31 vs. 1.33). Additionally, when they calculated total lifetime applications (based on years of use and frequency of application), their data was sinusoidal, fluctuating up and down with 1-5 years of daily use being significant but > 5 -20 years of daily use being not significant and then > 20 years of daily use being significant. (Please see Table 1 from Cramer (2016) discussed below.) The internal inconsistencies of reporting that 5-20 years of use does not increase the risk of ovarian cancer but 8-19 years of use does result in an increased risk, calls into question the validity of the entire study. As responsible researchers, the authors cannot and should not cherry pick the findings that support their hypotheses and minimize the results that do not support their foregone conclusions.

Cramer (1999) suffers from the same pitfall, where despite reporting an OR of 1.6 (CI 1.18,2.15) for ever vs. never perineal use of talc, the authors also found that the more applications of talc per month, the risk of ovarian cancer becomes less significant, with < 30 applications per month doubling a woman's risk and then with 40+ applications per

month being not statistically significant (14). This back and forth with statistically significant findings at one dose and then not statistically significant findings at a higher dose completely contradicts what we know is the definition of a dose response. The risk should continue to increase (or at a minimum plateau) with more exposure, not become less significant, as in Cramer (1999) and (2016) (14,15).

As stated above, one of the most glaring deficiencies in the case-control literature has been the lack of demonstration of a consistent dose-response curve. Like any other environmental exposure, if talc is a causal agent in the development of ovarian cancer, then there should be a clear dose-response curve with increasing exposure to talc leading to an increased risk of developing ovarian cancer. Langseth (2008) published a meta-analysis of the available literature as of that date, which consisted of 20 case-control studies and one cohort study (48). The authors noted specifically that 10 of the case-control studies reported statistically significant increased risks and the remaining 10 studies reported non-statistically significant risks, with several of the studies unable to establish a dose-response curve with exposure to talc in terms of either frequency of applications or length of use in years (4,6,10,14,59,88). They also reported “the main epidemiological evidence against the association [between talc and ovarian cancer] is the absence of clear exposure-response associations in most studies.” Additional, more recent studies that have also failed to demonstrate a clear dose-response curve include Penninkilampi (2018), Schildkraut (2016), Terry (2013) and Wu (2009) (62,72,79,91).

Another interesting observation from the Langseth paper was that while 10 of the 14 case-control studies that were conducted as population-based studies reported a statistically significant increase in the OR for the development of ovarian cancer with talc use in the perineal area (see table below), none of the hospital-based studies reported statistically significant results, both individually (6/6), and collectively as a meta-analysis (OR 1.12; CI 0.92,1.36) (48).

J Epidemiol Community Health 2008;**62**:358–360

Research report

Perineal use of talc and risk of ovarian cancer

H Langseth,¹ S E Hankinson,² J Siemiatycki,³ E Weiderpass^{1,4,5}

¹The Cancer Registry of Norway, Institute of Cancer Research, Oslo, Norway; ²Department of Biostatistics, Harvard Medical School, Boston, MA; ³Department of Social and Clinical Medicine, University of Montreal, Montreal, QC; ⁴Department of Epidemiology, Karolinska Institute, Stockholm, Sweden; ⁵Folkhälsan, Helsinki, Finland

Correspondence: E Weiderpass, Cancer Registry of Norway, Oslo, Norway; e-mail: eweiderpass@krh.no

Accepted 15 May 2008

Research report

Study (ref) country

OR [95% CI]

Population-based

Cramer	(11)	USA	1.61 (1.04 to 2.49)
Harlow	(15)	USA	1.10 (0.70 to 2.10)
Harlow	(16)	USA	1.50 (1.00 to 2.10)
Chen	(17)	China	3.90 (0.90 to 10.60)
Cramer	(20)	USA	1.60 (1.20 to 2.10)
Purdie	(21)	Australia	1.27 (1.04 to 1.54)
Chang	(22)	Canada	1.42 (1.08 to 1.86)
Cook	(23)	USA	1.50 (1.10 to 2.00)
Green	(24)	Australia	1.30 (1.10 to 1.60)
Godard	(25)	Canada	2.49 (0.94 to 6.58)
Cramer	(26)	USA	1.60 (1.18 to 2.15)
Ness	(28)	USA	1.50 (1.10 to 2.00)
Mills	(29)	USA	1.37 (1.02 to 1.85)
Jordan	(30)	Australia	1.16 (0.83 to 1.62)
Pooled OR for population-based studies			1.40 (1.29 to 1.52)

Hospital-based

Hartge	(12)	USA	2.50 (0.70 to 10.00)
Whittemore	(13)	USA	1.45 (0.81 to 2.60)
Booth	(14)	UK	1.30 (0.80 to 1.90)
Rosenblatt	(18)	USA	1.00 (0.20 to 4.00)
Tzonou	(19)	Greece	1.05 (0.28 to 3.98)
Wong	(27)	USA	1.00 (0.80 to 1.30)
Pooled OR for hospital-based studies			1.12 (0.92 to 1.36)

This finding has been interpreted as overt evidence of the recall bias that is inherent not just in the case-control studies on talc and ovarian cancer, but in all case-control studies. People who have had more time to perseverate and consider every detail and aspect of their lives that may have factored into how they developed a certain disease state, in this case ovarian cancer, are much more likely to report, if not over-report, a positive association with a certain exposure as they search for answers as to what may have caused them to be diagnosed with this condition. Use of talcum powder is self-reported data and is subject to recall bias, especially for factors such as the number of times of use per month and years of use. Additionally, the data can be influenced by the investigator in terms of the manner in which a question is asked or by the explanation of the intent of the study. This bias is inherently much stronger for case-control studies over any other study design, as the women selected as cases have necessarily been diagnosed with ovarian cancer in order to be selected for the study.

Finally, as we consider additional biases that impact the scientific literature on the relationship between talc and ovarian cancer, we must address the times we live in and social media and the bombardment of that media by the ubiquitous publicity of talc litigation. Schildkraut (2016) analyzed their results by subjects interviewed before and

after 2014 (when the media began heavily reporting about talc litigation) (72). The authors found that in women with ovarian cancer who were interviewed in 2014 or later, any reported use of talc was 12% higher than in women interviewed prior to 2014. This change in reporting rate resulted in an OR that was not statistically significant at 1.19 (CI 0.87,1.63) prior to 2014, rising to a statistically significant result of 2.91 (CI 1.70, 4.97) after 2014. Additionally, a test for the influence of year of reporting was found to be statistically significant and the authors offer that misclassification exists in case-control studies such as this, especially due to heightened awareness and publicity surrounding the lawsuits. Recognizing the influence and potential for biases introduced into their study by the talc litigation, the authors specifically analyzed their data in terms of prevalence of use and year of interview, pre- and post-2014. Recall bias and reporting bias were in fact documented by these authors, resulting in the inflation of the odds ratio from a non-statistically significant value to a statistically significant one, almost 2.5 times higher (72). This is an especially stark finding that validates the suggestions of authors well prior to 2014 that recall bias could be driving the results of case-control studies of talc and ovarian cancer.

Cohort Studies

Three independent cohort studies have been published on the potential relationship between talc and the development of ovarian cancer. One of these studies (Gertig (2000)) published a follow-up study, with additional data accrual, 10 years later (25,24). Each of these studies has enrolled large numbers of women who were asked questions about their genital use of talc and were then followed to see if they developed ovarian cancer. Because these women were followed prospectively, these studies are more scientifically credible, as by design they have removed the selection and recall biases of the case-control studies.

The Nurses' Health Study (NHS) enrolled 121,700 registered nurses starting in 1976. Every two years, the women were sent a questionnaire to update, and in 1982, they were asked questions about their perineal exposure to talc (25). The frequency of use was ascertained by asking women if they were never-users, daily, one to six times per week, or users of talc in the perineal area < 1 day/week. Forty percent of the cohort (31,789 women) reported ever-use of talc. The study cohort was then followed for 14 years. Confirmation of the diagnosis of ovarian cancer was made by obtaining medical records from any of the subjects that reported that they had been diagnosed with the disease. This study found that there was no association between the ever-use of talc in the perineal area and the development of ovarian cancer with a RR of 1.09 (CI 0.86,1.37). The authors also looked at the risk with different histologic subtypes of ovarian cancer and reported a modest increased risk for serous histology with ever-use of talc (RR 1.4; CI 1.02,1.91), but ever-daily use did not show the same statistically significant result (RR 1.49; CI 0.98,2.26), demonstrating the lack of a dose-response curve. Central to the hypothesis that genital talc use causes ovarian cancer is the theory that the talc migrates up to the Fallopian tubes and lands on the ovaries. If this is indeed true, then women who used talc and never had a tubal ligation should be at an

increased risk of developing ovarian cancer over never-users. To evaluate this hypothesis, the authors performed the analysis on the data after the women with tubal ligations and/or hysterectomies were removed from the data set and found that women who had ever-used talc and had not had a tubal ligation and/or hysterectomy were not at an increased risk of developing ovarian cancer (RR 1.15; 0.89,1.49) (25).

In order to further evaluate the modest association seen with the serous subtype and the perineal use of talc, the authors published a follow-up study 10 years later (24). This study did not ask any additional questions on perineal exposure to talc, but it did allow for more time to pass (24 years in total), which improves the latency and increased the ovarian cancer case count (from 307 to 797), which should substantiate any association between talc and the development of ovarian cancer, if one exists. Importantly, the previously reported association between serous cancers and genital talc use did not withstand the test of time, with the association not being statistically significant with the RR 1.06 (CI 0.84,1.35) in this follow-up study. Consistent with the earlier publication, there remained no statistically significant association between women who used talc perineally > once/week and the development of any histology of epithelial ovarian cancer, even with the passage of an additional 10 years of time and the diagnosis of an additional 490 cases of ovarian cancer (RR 1.06; CI 0.89,1.28). A criticism that is often made of these two studies is that they only ascertained information on talc usage at one point in time. We know from Wu (2015), however, that in women who are ever-users of talc in the perineal area, the mean duration of use is greater than 20 years (92). This means that even though the question regarding the application of talc that was asked in this study was a snapshot in time, the data that were collected on talc application in the perineal area reflected chronic, habitual use.

The Women's Health Initiative (WHI) Study collected data from 61,576 women on their use of talc in the genital area and then examined whether or not there was an association with the development of ovarian cancer (38). The women were asked questions on whether or not they had ever used talc in the genital area, and if they replied yes, they were asked specific questions about the duration of use (<1 year; 1-4 years; 5-9 years; 10-19 years; >= 20 years). As cases of ovarian cancer were self-reported, medical records were requested and adjudicated centrally by the WHI. After a mean follow up of 12.4 years, this study reported that there was no statistically significant association between the use of talc in the genital area and the development of ovarian cancer for ever-users (HR 1.13; CI 0.93,1.37), or for women that reported genital use of talc for 20 years or more (HR 1.10; CI 0.82,1.48). Additionally, there was no trend of increased risk with increasing duration of use with women who used talc in the genital area for 10 or more years having a HR of 0.98 (CI 0.75,1.29) compared to women that used talc for < 9 years with a HR of 1.24 (CI 0.99,1.55), with neither value demonstrating statistical significance. One of the criticisms of the WHI study that is often made by plaintiffs' experts in talc litigation is that the follow-up period for these patients was simply too short to have confidence in the conclusions. Both Drs. Blair-Smith and Wolf make this claim in their reports, stating, "all of the cohort studies are

limited by...short follow-up" (Smith p. 16; Wolf p. 8). I do not think this is a valid criticism, for two reasons. First, the women who were enrolled in this study were the exact age range of the majority of the women that develop ovarian cancer. Study subjects were 50-79 years old at enrollment with a mean age of 63.3, and as discussed above, the mean age of diagnosis of ovarian cancer is 63 years old. Additionally, these women were followed for another 12.4 years, which translates to the study subjects being 62-91 years old at the conclusion of the study. If a disproportionate number of cases of ovarian cancer were going to develop, it would be in this exact population. Second, the latency period of this study should not be assumed to be the same as the follow-up period of 12.4 years. The latency period is defined as the time from which the women were exposed to the environmental agent, specifically in this case, talc applied perineally, through the entire time of the study period. At the time of the conclusion of the study, the subjects that reported talc use in the genital area for more than 20 years did not demonstrate a statistically significant increased risk of developing ovarian cancer (HR=1.10; CI 0.82,1.48), and they had a latency period of 30+ years. The findings from the WHI study are scientifically sound not only because the study examines the age-appropriate population, but also for the long latency period that it reports upon, with the time of exposure beginning many years prior to the time of data collection.

The Sister Study identified 41,654 women between the ages of 35-74 who had a sister diagnosed with breast cancer (27). The women in this cohort are known to be at a higher risk of developing ovarian cancer, as they have a first-degree relative with breast cancer. The women were then asked about whether or not they had used talc in the genital area in the prior 12 months and about their frequency of use. Cases of ovarian cancer were confirmed by examining either medical records or death certificates. The authors reported that there was no statistically significant association between the perineal use of talc and the development of ovarian cancer (HR 0.73; CI 0.44,1.2). The hazard ratios reported did not change even when the women with BRCA mutations were excluded from the analysis; however, these women represented a small fraction of the study subjects. Although the mean time of follow up in this study was shorter than the other cohorts, and as a result, the latency period for this study is shorter than the other studies, the results of this study are still informative. The mean age of the study subjects was 55, with 55% of the controls and 69% of the cases being postmenopausal. As stated above, this study population is the same age range as the women who develop ovarian cancer in the general population. Additionally, of the women who reported genital use of talc within the prior 12 months, they most likely became regular users of talc around 20 years old, (according to Cramer (2016) (15)), meaning that the latency period of this study is at least 20+ years.

Collectively, the cohort studies do not demonstrate any statistically significant, consistent association between the genital or perineal use of talc and an increased risk of developing ovarian cancer. Additionally, these studies contained information on years of exposure or frequency of use and there is no evidence from any of these studies of a dose-response curve with either longer periods of use or more perineal

applications of talc. The risk of ovarian cancer did not increase with more exposure, as we would expect to see with any environmental agent that is thought to have a causative role in the development of a cancer. Further, these studies refute the proposed mechanism of exposure of the ovaries to talc via retrograde migration, as when women who had tubal ligations and/or hysterectomies were pulled from the analysis, the relative risk for developing ovarian cancer in ever users of talc in the perineal area remained unchanged and not statistically significant (24,38).

Meta-Analyses and Pooled Analyses

Several meta-analyses have been published on the proposed relationship between the perineal application of talc and the development of ovarian cancer. In addition, there have been a few published pooled analyses; two are independent and another is found within the discussion sections of one of the case-control studies (14,48,79). The majority of these studies combine the data from any number of the previously published case-control studies in an attempt to demonstrate a more robust and statistically significant association. One of the more recent meta-analyses has also included data from some of the cohort studies, but strangely, the authors chose to use the NHS 2000 study and not the 2010 study (62). The reported rationale for this lack of inclusion was to not have duplicate data as part of the study. While that intended aim is valid, the authors fail to disclose why they chose the earlier study over the later when the later study clearly has an increased latency and more statistical relevance. As stated previously, since the meta-analyses and pooled analyses are essentially compilations of the original publications, they are subject to the same weaknesses and biases that were embedded in the smaller original studies. Additionally, because not all of these original case-control and cohort studies were conducted in the same manner, or asked the study subjects the exact same questions, the merging of the data presents some problems. When considered as a group, the meta-analyses and pooled analyses report modest increases in the risk of developing ovarian cancer with the genital use of talc in the range of an odds ratio of 1.24 to 1.4. Because this is exactly the range that is reported in the case-control studies that report a positive association, grouping the studies together did not lead to any more strength in the association. Importantly, neither the meta-analyses nor the pooled analyses could establish a dose-response curve with the pooling of the data. None of the studies reported positive findings for any increasing length of time of use (be it duration, or frequency or increasing number of lifetime applications), and they could only achieve a modest statistically significant increase in risk for ever-users compared to never-users (3,62,79). Much has been made about the supposed inter-study consistency of the relative risks reported by the meta-analyses by plaintiffs' gynecologic oncology experts. This finding is no great surprise since the meta-analyses used many of the same case-control studies in their analyses. Collectively across their expert reports, Drs. Clarke-Pearson, Wolf and Blair Smith cite eight systematic reviews. The earliest meta-analysis cited in the reports of plaintiffs' gynecologic oncology experts is a composite of six studies published in 1992 (34). In 1995, Gross and Berg published another meta-analysis that used all six of the studies from the 1992 study and added three more, but then in 1999, these nine studies were re-hashed into another meta-

analysis with an additional five studies (14,31). With the more recent publications of Penninkilampi and Berge, the percentage of overlapping studies is even higher (62,3). Both of these studies analyzed 24 case-control studies, 19 of which they share in common. Table 2 details the eight systematic reviews cited by plaintiffs' gynecologic oncology experts and the significant overlap of case-control studies amongst them (62,3,79,48,39,14,31,34). Given the fact that these seven meta-analyses and one pooled analysis are using shared data sets and simply re-working the same information, it is expected that they all report similar relative risks. As such, despite plaintiffs' experts' assertion to the contrary, the number of meta-analyses and the similarity in the reported relative risks does not add any strength to plaintiffs' theories.

In summary, the epidemiologic literature on the association between the use of talc in the genital area and the development of ovarian cancer does not support a causal role for talc. The case-control studies are inconsistent, both between studies and within individual studies and they are unable to demonstrate a dose-response curve; the cohort studies do not demonstrate any statistically significant associations across the tens of thousands of women studied over decades and they undermine the hypothesis of biologic plausibility; and lastly the meta-analyses bring nothing new to the discussion, again rehashing the same data many times over and still being unable to demonstrate any changes in the purported strength of association or any evidence of a dose-response curve.

Migration of Talc from the Perineum to the Ovaries

Integral to the hypothesis that genital application of talc causes ovarian cancer is the theory that talc can migrate from the perineum to the ovaries. Many of plaintiffs' experts have taken this as a given, and even the U.S. Food & Drug Administration has stated, "While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable" (20). Cited as support for this hypothesis of migration is the finding by Heller (1996) of talc particles in the ovaries of 12 women that reported perineal use of talc (37). The problem with this logic is that talc was also found in the ovaries of 12 women who reported never using talc in the perineal area, and the talc counts did not at all correlate with the reported exposure history. No one actually knows how the talc that is found in pathology samples gets there. The presumption is that because some researchers have conducted studies whereby they have placed particulate matter into the vagina, be it carbon particles or radio-labeled albumin microspheres, and later found evidence of these substances in the ovaries, talc must be able to migrate from the perineum to the ovaries as well (17,84). But the vagina is not the perineum and the female genital tract is not an open conduit, despite Drs. Clarke-Pearson and Smith-Bindman's contrary contentions in their depositions.

Plaintiffs' expert Dr. Clarke-Pearson asserts that "there's no lid at the opening of the vagina," making it "open to the outside world, if you will" (p. 89). Dr. Smith-Bindman reports that she can study tubal patency by placing fluid on a woman's perineum, but then later qualifies that statement by admitting that she is actually "putting water into the uterus" (p. 370), where the Fallopian tube ostia originate. She then goes on to contend that in patients in whom she cannot catheterize the cervix, or where she may be "looking for connections between different structures" that she can simply put "the tube directly on the perineum and see if we can create kind of a - -a way to keep, let's say, a balloon in place and then inject" (p. 371). This is a preposterous description of the studies that are done to examine a woman for a fistula, perhaps between the vagina and the bladder and/or the rectum. It is absolutely impossible to study the Fallopian tubes and ascertain their patency in this manner. The perineum is on the outside of a woman's body. It is not a cavity that would accommodate a balloon, nor would it contain contrast material and allow enough pressure to be generated to direct the contrast into the vagina, let alone the bladder, the uterus or the rectum. To study these organs, you need to put the contrast directly into them – not on the outside surface of the body. As a clinician who is subspecialty trained and has been practicing in the field specializing in female genital anatomy, I am confident that Dr. Smith-Bindman is wrong. Dr. Smith-Bindman even acknowledged that, whatever the details of the procedure she described, it had to include placement of water or fluid into the vagina, which is obviously beyond the external perineum (p. 371).

These suggestions by Drs. Clarke-Pearson and Smith-Bindman grossly mischaracterize female reproductive anatomy. There are many barriers between the external female genitalia and the ovaries, all intentionally evolved to keep the endometrial cavity and the peritoneal cavity (where the ovaries reside) sterile and separate from the non-sterile external environment. For some particulate matter to reach the ovaries from the perineum it would need to get past the labia majora (which are naturally opposed and close off the inner vestibule). The particle would then need to pass between the opposed labia minora, across the perineal body, through the introitus, up into the vagina and traverse the 7-9 cm of the vagina, and all the while not get washed away by vaginal secretions. From there, the particle would need to navigate into the cervical canal through the 4-5 cm cervix and the tenacious cervical mucous, into the endometrial cavity, across 5 cm or so of the uterus and into the opening (ostia) of the Fallopian tube, travel the entire length of the Fallopian tube to the fimbria and then land on the ovaries. The female genitalia are designed to prevent such an ascension, as it is important to every woman's health that multiple barriers be in place to prevent easy passage of foreign substances on a regular basis. The female genitalia are not simply open to the external environment. Furthermore, the hypothesis that retrograde ascension is the pathway by which the talc is gaining access to the ovaries is purely speculative and there is no data to support it. Not a single human study has ever been published that has actually documented the migration of particulate matter from the perineum all the way to the ovary.

Inflammation as the Mechanism by which Talc Induces Ovarian Cancer

Several hypotheses have been proposed as to what leads to malignant transformation in the ovary. There is the incessant ovulation hypothesis that suggests that the chronic disruption of the surface of the ovary by the process of ovulation can cause enough damage to the surface epithelium that the cells become cancerous (19). Others have proposed that it is not the actual disruption that leads to the malignant transformation, but rather the entrapment of the surface epithelium into crypts deep within the ovarian stroma and the epithelium's subsequent exposure to high hormone levels, including estrogens, that is carcinogenic. Plaintiffs' experts have proposed that talc causes chronic inflammation, which leads to the development of ovarian cancer. The epidemiologic and biologic data, however, do not support the hypothesis that chronic inflammation plays a role in causing ovarian cancer. First, as a practicing gynecologic oncologist for more than 20 years, I have a great deal of experience operating on patients with ovarian cancer. I do not see evidence of an inflammatory process when I am operating on patients with this diagnosis. There is no evidence of adhesions or scar tissue within the abdominal cavity, and on microscopic examination of the tissues, there is no evidence of activation of an inflammatory cascade. We also do not see granulomas or foreign body giant cell reactions, which are present when the body invokes a chronic inflammatory response in response to a foreign substance.

Second, pelvic inflammatory disease (PID) is not associated with the development of ovarian cancer. PID is a condition whereby the uterus, tubes and ovaries are involved in an inflammatory response as a result of a sexually transmitted disease that ascends the upper genital tract after sexual intercourse. The inflammatory response can result in abscess formation, development of scar tissue and infertility. Proponents of the hypothesis that ovarian cancer results from chronic inflammation have examined the relationship between PID and the development of ovarian cancer. A few small studies have reported inconsistent results in the past. More recently, a large pooled analysis of 13 case-control studies with 11,966 women with invasive and borderline ovarian tumors was published (66). This study demonstrated no association between a history of PID and ovarian cancer risk (OR=0.99; CI: 0.83-1.19) and only women with at least two reported episodes of PID had a two-fold increased risk of borderline tumors. This lack of association between a chronic inflammatory condition such as PID and ovarian cancer demonstrates the lack of clinical data to support inflammation as the mechanism of malignant transformation in the ovary. Additionally, if talc really is migrating across all these intermediary organs and causing chronic inflammation, then we would see evidence of an increased risk of cancers developing in the vagina, the cervix and the endometrium – and we do not. One of plaintiffs' experts (Dr. Crowley) has stated that since the vagina and the eye are both mucous membranes, that what irritates the eye is also very likely to irritate the vagina (p. 12). While the surface of both the vagina and the conjunctiva are composed of the same cell type, the similarities in their composition ends there. The conjunctiva is a thin covering of the eye, composed of a single layer of

basal cells and 4-5 layers of squamous epithelium (29). The vagina, however, is much thicker, with the deep layer having the basal and parabasal cells, the intermediate layer is typically 10 cell layers thick and then the superficial layer is roughly the same thickness and composed of about another 10 cell layers. The vaginal mucosa then accords into numerous folds, called rugae, which gives the vagina much flexibility and pliability (73). The vaginal mucosa is designed to withstand many environmental exposures (e.g., sperm, the products of childbirth, bacteria), which the conjunctiva would never endure.

Lastly, if talc induces ovarian cancer by causing chronic inflammation, then studies examining the use of anti-inflammatory agents such as NSAIDs and aspirin should show a decreased risk of developing ovarian cancer with regular use of these agents. The epidemiologic literature that has examined this question has not shown a consistent reduction in the risk of ovarian cancer with the use of NSAIDs, and this includes studies that also examined the risk of perineal application of talc (13,15,91). In the Nurses' Health Study (2018), results on the use of analgesics and the risk of ovarian cancer demonstrated inconsistency in terms of dose response as low-dose aspirin appears to decrease the risk of developing ovarian cancer, whereas standard dosing demonstrates no association and the use of non-aspirin NSAIDs showed an increase risk of developing ovarian cancer, although not statistically significant (2). The gynecologic oncology community does not recommend the use of NSAIDs to patients as a risk-reducing strategy for the development of ovarian cancer as we recommend the use of oral contraceptive agents.

Summary

There is no literature that particulate matter such as talcum powder, applied to the perineum, can migrate to the ovaries. The link between talc exposure and ovarian cancer is unproven, as there is inconsistency in the detection of talc in the ovarian tissue of women who reported heavy use or no use at all. The clinical and epidemiologic data do not support the hypothesis that talc causes ovarian cancer through the induction of a chronic inflammatory process, primarily because there are no data to support that inflammation is underlying the malignant transformation of the ovarian epithelium at all.

Talc as the Vehicle by which Other Substances Can Cause Ovarian Cancer

An additional hypothesis that has been floated by plaintiffs' experts in this litigation is the theory that cosmetic talcum powder is either contaminated by certain substances or has been mixed with substances that are the actual cancer-causing agents. The substance that has received the most attention in this arena is asbestos. In 2012, IARC (the International Agency for Research on Cancer) released a monograph on asbestos in which the Working Group noted a causal association between heavy occupational

exposure to asbestos and cancer of the ovary (41). IARC classifies asbestos as a Group 1 agent, meaning that it is carcinogenic to humans, but notably, the perineal application of talc is in Group 2b, meaning that there is only limited evidence of carcinogenic potential in humans and so it is listed only as *possibly* carcinogenic (40).

The IARC working group conceded in the asbestos monograph that there was a paucity of data to examine and that its conclusions were based upon five published studies that showed any statistical significance, because all of the other studies on women that involved environmental exposure, and not heavy occupational exposure, did not achieve statistical significance (41). There are several problems with the conclusion that IARC has drawn. First is the problem of misclassification. The studies that were published used data from death certificates, not prospective medical records or an examination of the actual tumors. It is quite possible that the subjects in the studies cited in the monograph actually had peritoneal mesothelioma (a disease known to be caused by asbestos), not ovarian cancer, as these two diseases have historically been difficult to distinguish clinically. From a pathologic standpoint, the distinction can be made by examining the individual tumor immune profiles and by systematically examining immunohistochemistry markers (78). Much of this technology was not available in the 1980s and 1990s, when three of the five studies cited by IARC were published. Additionally, none of the studies cited in the IARC monograph controlled for other risk factors known to be associated with ovarian cancer development. Langseth (2007) examined the ovaries of women who worked in the paper and pulp industry, employment known to be associated with occupational exposure to asbestos (47). The authors identified 31 cases of ovarian cancer for which tissue was available and compared them to 86 control subjects (41 with cancer and no exposure and 45 with no cancer and no exposure). Only two of the cases were found to have asbestos in their ovaries, and one of these women was not actually working with asbestos, meaning that she possibly had second-hand exposure. None of the control subjects had asbestos in her ovaries. The authors conclude that asbestos does not contribute as a causal factor in the development of ovarian cancer in either women with occupational exposure to asbestos or in the general public.

Asbestos is ubiquitous in the environment, as asbestos fibers can be found in the ovaries of women with documented household exposure as well as in women with no reported history of asbestos exposure (36). This does not necessarily mean, however, that the asbestos migrated retrograde from the perineum through the genital tract to the ovaries. The path of migration has not been established in either men or women. Autopsies on patients with a large number of asbestos fibers in their lungs also found asbestos fibers in nine different organs, meaning that they could have passed into the blood or lymphatic system and were deposited at different sites (47). Regardless of how the asbestos migrated to the ovaries, the balance of the evidence does not support a causal role for asbestos in the development of ovarian cancer.

If talc is the vehicle by which the proposed carcinogen (e.g., asbestos) is being delivered to the ovaries, then the epidemiologic literature on perineal application of talc and the development of ovarian cancer should be consistent and scientifically credible. And it is not. My opinion does not change regardless of the composition of the talcum powder because the published, peer-reviewed literature does not support an increased risk of developing ovarian cancer with perineal application of talc.

Summary

I have been practicing in the field of gynecologic oncology since 1995. During my training and throughout my academic practice, I have emphasized the importance of assessing risk factors for the development of ovarian cancer. There are risk factors that are well established and consistently supported by the scientific literature and by the observations made in the clinical practice of medicine. These include age, genetic predisposition, family and personal history of cancer, reproductive factors and postmenopausal hormone replacement therapy. Other factors that are less impactful and tend to be more associated with specific histologic subtypes of ovarian cancer include endometriosis, tobacco use and obesity. Factors that appear to decrease a woman's risk of developing this disease include use of oral contraceptives, tubal ligation, breastfeeding and prophylactic surgery. After thorough review and consideration of all of the available data, it is my opinion that the perineal application of talc is not a risk factor for the development of ovarian cancer. This opinion is based on the inconsistencies within the epidemiologic literature, the absence of a dose-response relationship, the lack of biologic plausibility for a mechanism of migration and no clinical data that inflammation is involved in the development of ovarian cancer.

Plaintiffs' Experts Engage in Speculation and Selective Reviews of the Literature

Plaintiffs' experts cherry-pick the literature that they use in their analyses and dismiss studies that do not support their opinions to give the false impression that there is consistency in the published literature. As discussed above, 54% of the case-control studies did not show a statistically significant increased odds ratio of developing ovarian cancer with the genital use of talc, and in all of these studies the odds ratio was always below 2.0 (Table 1). Yet, Dr. Wolf states in her report that the "magnitude of risk has been consistent over three decades," and the "results are generally consistent across case-control ... studies." (p. 15). Dr. Blair Smith adds that "the consistency of the case-control epidemiologic studies ... is impressive" (p. 20). Both of these experts are dismissive of the contribution of the cohort studies, with Dr. Wolf stating that the WHI study does not include information "regarding the frequency or duration of powder usage" (p. 7). This is simply not true, as the study collected incremental data on the duration of use from < 1 year to >= 20 years. Additionally, she claims that this study was subject to "recall bias regarding history of talc 'ever use'" (p. 7). If any type of

epidemiologic study is subject to recall bias, it is the case-control studies, because, as explained earlier in this report, they are inherently retrospective. In Schildkraut (2016), one of the case-control studies cited by all three of plaintiffs' gynecologic oncology experts, the authors conceded in the discussion section of that paper that some inflation of the reported ORs was likely due to the publicity surrounding the recent lawsuits (72). The authors reported that "[i]n 2014 and later, we observed an increase in any powder use of 12% and 6% of cases and controls, respectively... A test for effect modification by year of interview was statistically significant ($p=0.005$)."

On page 164 of his deposition, Dr. Clarke-Pearson admits that these findings in Schildkraut would be an example of the potential effect of recall bias. Any study that relies upon self-reporting has challenges in assessing an exposure, but the difference between the cohort studies and the case-control studies is that the former is asking the question in real time and then following the subjects forward and the latter is all about past events.

Plaintiffs' experts' criticisms of the studies that do not support their position are either erroneous or false. As discussed above, Dr. Wolf falsely claims that the WHI study did not collect data on duration of talc use in the perineal area and therefore she does not consider it relevant to her analysis (p. 7). Additionally, Dr. Wolf criticizes the NHS as having too short a follow-up time of 12.9 years and asserts that the "short period of follow up may not account for all ovarian cancer cases" (p. 7). She acknowledges that the Gates (2010) study, published 10 years later, is a continuation of the NHS, but does not consider that additional time in her analysis of the total latency period of the study; nor does she consider that the women in the study most likely started perineal usage of talc many years prior to study enrollment. Dr. Blair Smith critiques the WHI study as having a latency period of only "12+ years," but ignores that the study collected information on up to 20+ years of talc use, thereby making the latency period much longer than 12 years. Additionally, she claims that "no histologic information was obtained" (p. 15). This claim is simply false. Please see Table 4 from Houghton (2014), as inserted below, which details the hazard ratios by histologic subtype of ovarian cancer.

Perineal Powder Use and Risk of Ovarian Cancer

Serena C. Houghton, Katherine W. Reeves, Susan E. Hankinson, Lori Crawford, Dorothy Lane, Jean Wactawski-Wende, Cynthia A. Thomson, Judith K. Ockene, Susan R. Sturgeon

Manuscript received October 31, 2013; revised May 21, 2014; accepted June 5, 2014.

Corre
MA 0

Table 4. Age and multivariable-adjusted hazard ratios for combined ever powder use by subtype of ovarian cancer (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR*	Multivariable HR*
			(95% CI)	(95% CI)
Serous†				
Never	87	355 523	1.0 (referent)	1.0 (referent)
Ever	117	404 983	1.18 (0.89 to 1.56)	1.16 (0.88 to 1.53)
Serous Invasive				
Never	80	355 523	1.0 (referent)	1.0 (referent)
Ever	105	404 983	1.16 (0.87 to 1.55)	1.13 (0.84 to 1.51)
Mucinous				
Never	12	355 523	1.0 (referent)	1.0 (referent)
Ever	13	404 983	0.98 (0.44 to 2.14)	1.03 (0.47 to 2.27)
Endometrioid				
Never	13	355 523	1.0 (referent)	1.0 (referent)
Ever	20	404 983	1.39 (0.69 to 2.79)	1.29 (0.64 to 2.61)
Other				
Never	47	355 523	1.0 (referent)	1.0 (referent)
Ever	54	404 983	1.04 (0.71 to 1.54)	1.04 (0.70 to 1.54)

Dr. Clarke-Pearson does not even discuss the cohort studies in his report, other than to generally mention that they, along with the case-control studies, “are compelling” (p. 7). He admits in deposition testimony that he excluded the cohort studies from his discussion “because I don’t think they contribute one way or the other” (p. 145) and he also concedes that he “overlooked adding Berge” to his list of meta-analyses (p. 178). Responsible reviews of the literature that are intended to evaluate whether or not there is an association between the use of talc in the perineal area and the development of ovarian cancer cannot, and should not, ignore entire segments of the epidemiologic literature, or make false claims about the studies that do not support a foregone conclusion.

Plaintiffs’ experts rely too heavily upon meta-analyses that review essentially the same biased studies. Dr. Blair Smith comments on the uniformity of the meta-analyses as being “impressive” (p. 20). Dr. Clarke-Pearson reports on the OR = 1.31 in Penninkilampi (2018), noting that “every meta-analysis before 2018 also reported similar increase in the risk of developing EOC with the use of talcum powder” (p. 8). And lastly, Dr. Wolf writes that the “magnitude of risk has been consistent over three decades, across various geographic populations,” citing Penninkilampi (2018) (p. 15). As explained earlier in this report, it is not surprising that the meta-analyses are all reporting similar results when they draw from many of the same case-control studies for the pooling of the data (Table 2). This is not consistency; it is simply repetition. More recently, two of the meta-analyses have added data from three of the cohort studies (3,62). Glaringly absent from the Penninkilampi paper, however, are the data from Gates (2010), which is the ten-year follow-up data from the original NHS publication by Gertig (2000). The authors contend that they did not include the Gates (2010) data so as to not have duplicate entries, but it is unclear why they did they not use the data from the later study, which extends the latency period by 10 years (Gates (2010)) and

eliminate the earlier study (Gertig (2000)). An additional criticism by plaintiffs' experts of the cohort studies is that they are not sufficiently powered to detect a modest increase in risk. This assertion is simply unsubstantiated by the actual science. In Berge (2018), the authors performed separate meta-analyses by study design (case-control vs. cohort) and they were able to demonstrate that "the statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as [an] explanation of the heterogeneity of results" (3). It is notable that in both Penninkilampi and Berge, when the data from the case-control studies were analyzed separately from the pooled cohort data, only the analysis from the case-control studies showed a statistically significant increase in risk, with the cohort studies not demonstrating such an association, whether or not the data from the Gates study was omitted, as was the case in the Penninkilampi study (3,62).

Plaintiff's experts' claims of a dose-response gradient are not substantiated by the literature they cite. A dose-response gradient, or curve, refers to an exposure-response relationship whereby with increasing exposures, the magnitude of the response will be even greater. In the case of genital use of talc and the development of ovarian cancer, this relationship is not borne out in the literature. In their reports, all three of plaintiffs' gynecologic oncologists cite Terry (2013), Penninkilampi (2018), Schildkraut (2016) and Cramer (2016) as supportive evidence that there is a dose-response curve, but not one of these studies actually demonstrates such a relationship (79,62,72,15).

Terry (2013) is a pooled analysis of eight case-control studies in which the only significant finding was a comparison of ever use with never use. The authors report that "although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis, no trend in cumulative use was evident in analyses restricted to ever-users of genital powder. Taken together, these observations suggest that the significant trend test largely reflects the comparison of ever-regular use with never use" (79).

Penninkilampi (2018) utilized only 5/24 of the case-control studies and none of the cohort studies identified in its analysis to examine the risk of developing ovarian cancer with <3600 total lifetime applications vs. > 3600 applications. The authors reported a slightly greater increased risk of ovarian cancer with > 3600 applications (OR 1.32; CI 1.15,1.50), but this number was not statistically significantly different from the OR reported for > 3600 applications (OR 1.42; CI 1.25,1.61). There is no dose-response gradient if the risk does not change with increasing exposure (62).

Schildkraut (2016) is a population-based case-control study that also examined risk as defined by <3600 applications vs. >= 3600 applications in addition to examining the differences in risk with exposure < 20 years vs. >= 20 years. The women exposed to talc for < 3600 applications or for < 20 years did not have a statistically significant increased

risk of developing ovarian cancer. This means that in comparing the lower exposed women to the women with ≥ 3600 total applications or exposure for ≥ 20 years, the comparison being made is essentially never users to ever users and does not constitute a dose-response gradient (72). This is essentially the same confounding observation pointed out by Terry (2013), whereby without a trend in cumulative use, the statistically significant finding at ≥ 3600 total applications or exposure for ≥ 20 years and not at lower doses, is really just a reflection of ever regular users with never users.

Cramer (2016) is a case-control study that pooled data from three separate prior enrollment phases. The study collected data on frequency of talc use in terms of number of days used per month and months per year as well as duration data by number of years used. The authors also made calculations to estimate number of lifetime applications from the frequency and duration data. The authors reported an increasing risk with an increased number of days used per month. The data on increasing risk and number of years used, however, was flat, with the risk for < 8 years (OR 1.31; CI 1.03, 1.68) being the same as the risk for > 35 years (OR 1.33; 1.03, 1.71) (Table 1 from Cramer (2016)).

ORIGINAL ARTICLE

OPEN

The Association Between Talc Use and Ovarian Cancer

A Retrospective Case–Control Study in Two US States

Daniel W. Cramer,^{a,b} Allison F. Vitonis,^a Kathryn L. Terry,^{a,b} William R. Welch,^c and Linda J. Titus^d

Cramer et al.

Epidemiology • Volume 27, Number 3, May 2016

Background
have led onl
greater clarit

TABLE 1. Type, Timing, and Duration of Genital Talc Use

	Control Subjects N (%)	Case Subjects N (%)	Adjusted* OR (95% CI)
Frequency of use			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
1–7 days per month	220 (11)	227 (11)	1.17 (0.96, 1.44)
8–29 days per month	110 (5)	133 (7)	1.37 (1.05, 1.78)
≥30 days per month	205 (10)	267 (13)	1.46 (1.20, 1.78)
P trend			<0.0001
Years used			
Never used	1,551 (74)	1,399 (69)	1.00 (referent)
<8	133 (6)	152 (8)	1.31 (1.03, 1.68)
8–19	126 (6)	145 (7)	1.31 (1.02, 1.68)
20–35	147 (7)	178 (9)	1.35 (1.07, 1.70)
>35	129 (6)	152 (7)	1.33 (1.03, 1.71)
P trend			0.002
Months per year of use ^c			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
1–3 months per year	61 (3)	60 (3)	1.11 (0.77, 1.61)
4–11 months per year	55 (3)	56 (3)	1.13 (0.77, 1.66)
12 months per year	193 (10)	229 (13)	1.35 (1.09, 1.67)
P trend			0.006

The most inconsistent finding from this study, however, which actually refutes the claim of the existence of a dose-response curve, comes from the fact that data examining “Total genital talc applications” are inconsistent, and conflict with the data presented on “Years used”:

TABLE 1. (Continued)

	Control Subjects N (%)	Case Subjects N (%)	Adjusted* OR (95% CI)
Total genital talc applications (apps) among only those who reported months per year of use ^c			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	106 (6)	103 (6)	1.10 (0.83, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	79 (4)	96 (5)	1.38 (1.01, 1.88)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	61 (3)	63 (4)	1.16 (0.80, 1.66)
>7,200 apps (equivalent to >20 years of daily use)	63 (3)	83 (5)	1.49 (1.06, 2.10)
<i>P</i> trend			0.02
Total genital talc applications among all (assuming 12 months/year when missing months per year of use)			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	138 (7)	138 (7)	1.15 (0.89, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	124 (6)	148 (7)	1.36 (1.06, 1.75)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	124 (6)	156 (8)	1.41 (1.10, 1.80)
>7,200 apps (equivalent to >20 years of daily use)	149 (7)	185 (9)	1.39 (1.11, 1.75)
<i>P</i> trend			0.003

In this paper, the authors calculated a figure for what they called lifetime exposure by multiplying frequency of applications per month by months used. They then divided this number by 360 to yield what they called “talc-years” and reported this along with the number of total genital applications. As seen in Table 1 of the Cramer (2016) study above, this analysis demonstrated that one year of daily use was not statistically significant for increasing the risk of ovarian cancer; > 1-5 years of daily use has a statistically significant increased risk, but with >5-20 years of use the risk of developing ovarian cancer went down and was not statistically significant and then with >20 years of use, the risk went up and became significant again. This study also includes conflicting and inconsistent data, as in one section of Table 1, 8-19 years of use is shown to increase the risk of developing ovarian cancer, but later in the same table, 5-20 years of talc use, as calculated from total applications, does not demonstrate a statistically significant increase in risk (15). In deposition testimony, Dr. Clarke-Pearson admitted that there is “not a consistent” dose response in this publication (p. 192). Cramer (2016) does not establish the existence of a dose-response curve; nor does any of the epidemiologic literature.

Plaintiffs’ experts’ hypotheses of biologic plausibility are pure speculation. Previous sections of this report discuss why plaintiffs’ experts’ theories regarding retrograde migration through the female reproductive tract are inconsistent with what we know about female anatomy. In fact, some of plaintiffs’ experts seem to have gross misconceptions regarding the actual anatomy of the female genital tract. I discussed above how, if Dr. Smith-Bindman is really contending that she can simply apply fluid to a woman’s perineum and have it travel all the way through her Fallopian tubes, then her contention cannot be taken seriously. If this were true, then women who swim in the ocean would become hypernatremic (high sodium) and those who swim in pools would

become hyperchloremic (high chloride), from the simple passage of water from their perineum into their vagina and then into their peritoneal cavity to be systemically absorbed. Of course, this does not happen. Similarly, with Dr. Saed stating in deposition testimony that the “fallopian tube is very close to the uterus” (p. 169) (when it in fact originates there), one has to wonder if he has even the most basic understanding of female reproductive anatomy. He continues to testify that talc particles, if they make it to the ovaries, after all the “wash[es]” and “dilution factor[s]” and “always excretions” of the vagina, cervix and uterus, just sit there since the ovaries are not bathed in fluids (pp. 165-66). This description of the peritoneal cavity as a dry environment is without basis in science, as there is a constant bathing in peritoneal fluid of all intra-abdominal organs, including the ovaries.

The vagina is not the perineum, and no studies have ever shown that something placed onto the perineum can migrate to the ovaries. While plaintiffs’ experts discuss in their reports that the female reproductive tract is open to the external environment, there is not a single study that traces something from the vulva to the ovaries. Some of plaintiffs’ experts rely on the study by Drs. Egli and Newton published in 1961 to support the hypothesis that talc can migrate from the perineum to the ovaries (17). In this study, three women were placed under general anesthesia and positioned in a lithotomy position with their legs separated and raised and their heads tilted downward from the horizontal. A speculum was placed into the vagina in order to open it and a slurry of carbon particles was inserted into the posterior vagina. The women were given an oxytocin injection to induce uterine contractions. They then had surgery to remove their Fallopian tubes, which were inspected for the carbon particles. Carbon was found in the tubes of two of the three women and no carbon was identified in the tubes of the 3rd woman. The conditions under which the women in the Egli study were evaluated are not analogous to women placing talc on their perineum. Despite Dr. Blair Smith’s pronouncements that it is a “universally accepted phenomenon by the gynecologic medical community, well documented in the scientific and medical literature that the female genital tract functions as a conduit for foreign material to enter the peritoneal cavity,” (p. 17) and Dr. Carson’s claim in his deposition that the “transport time” for talc in the reproductive tract “is roughly the same for any particulate matter, including sperm” (p. 303), neither one of these individuals cites a single article in support. They are both offering opinions that are pure speculation with absolutely no data to substantiate these claims.

Plaintiffs’ experts also claim that ovarian cancer is caused by inflammation and that the talc induces this inflammatory process. Drs. Blair Smith and Wolf state that talc causes ovarian cancer analogous to the manner by which HPV causes cervical cancer, through an inflammatory process (Smith p. 21; Wolf p. 16). This is simply wrong. Infection with HPV leads to insertion of the viral DNA strands into the host DNA strands. The viral DNA is then replicated and translated, resulting in the production of several proteins, most importantly the oncoproteins E6 and E7. The carcinogenicity of HPV is attributed to the HPV oncoproteins E6 and E7, which immortalize and transform the host cells by

inactivating tumor suppressor proteins (p53 and pRB1), resulting in malignant transformation. There is no inflammatory cascade in this process of carcinogenesis. (67,82). Dr. Wolf further proclaims that the “general mechanism by which talcum powder products cause ovarian cancer is established as an inflammation-induced process” (p. 15), without citing any literature to support this position. Dr. Blair Smith states that the “general mechanism is not only plausible, but accepted widely – even though the details at the molecular level are still being clarified” (p. 20). This is speculative. The in vitro studies that purport to support the hypothesis that talc can induce an inflammatory response, which leads to malignant transformation in ovarian cells, have been published in journals with very low impact factors. The importance of scientific work is evaluated not only by the peer-review process, but also by the ranking of the journal in which that work is published. High-quality mechanistic cancer biology research would likely be published in *Cell* or *Nature*, which have impact factors in the range of 30 to 40, as that work is likely to be cited in other scientific articles. Dr. Saed’s most recent work has been accepted (without a proper conflict-of-interest disclosure) for publication in *Reproductive Sciences*, which has an impact factor of 2.4, reflecting low probability that this work will be cited in any other scientific publications (21). It is likely that his work is not being accepted into more prestigious publications because the reviewers for those more prestigious publications do not consider his science to be of the same quality or caliber as is typically published in those journals.

Dr. Saed’s research group has proposed that they have demonstrated the molecular basis of talc increasing the risk of ovarian cancer by demonstrating that ovarian and ovarian cancer cells in cell culture produce increased levels of CA 125 when treated with talc (21). This is not evidence of malignant transformation. Many things elevate the CA 125 level – pregnancy, fibroids, menstrual cycles. CA 125 is not a marker of risk for developing ovarian cancer; nor is it used to make a diagnosis and it is not used to determine the cause of ovarian cancer. CA 125 is a protein that is ubiquitous on epithelial cells and the cells shedding this antigen in response to the stress of being treated with talc does not mean that it is carcinogenic. Lastly, the epidemiological literature does not support this hypothesis, as studies have found inconsistency in terms of risk of ovarian cancer with use of aspirin and non-steroidal agents, with at least two studies reporting an increase in the risk with increasing frequency and duration of use (2,91).

Plaintiffs’ experts’ opinions on cancer genetics are speculative and unsupported. Dr. Levy postulates in his report (pp. 5, 8) and deposition (pp. 322, 324, 325) that inherited gene mutations can make individuals “more likely to develop cancer when exposed to certain cancer-causing substances,” including talc. But at his deposition, Dr. Levy was unable to identify any published scientific literature to support the theory that women with BRCA or TP53 mutations are somehow “more likely” to develop ovarian cancer as a result of talc use (pp. 325-26), and I am not aware of any. Similarly, although Dr. Levy maintains that talc is genotoxic, he admitted at his deposition that he is not aware of any study supporting that claim, instead resting on the fact that he is not aware of a

study that “has concluded that there are no genotoxic effects of any type of talc” (pp. 354-55). But this approach of apparently presuming that talc is genotoxic until proven otherwise is profoundly unscientific. The burden on the scientist is to prove the hypothesis, not assume the hypothesis is true until someone else disproves it.

Plaintiffs’ experts make broad, sweeping pronouncements that are hypothetical, without corroborating scientific data. Dr. Clarke-Pearson correctly contends that plausibility is a “critical factor when forming opinions on causation” (p. 9). He then goes on to state that an “inflammatory reaction caused by talcum powder on the tube and surface of the ovary results in genetic mutations and carcinogenesis. Talcum powder causes ovarian cancer through this mechanism” (p. 9). There is not one citation in this paragraph (or his entire report) that supports this proclamation or his contentions. Rather, his statements of “facts” are hypotheticals. No one has ever shown that talc (or any other particle for that matter) reaches the ovaries and tubes through ascension from the vulva, and certainly there is no data that talcum powder is mutagenic. In discussing coherence, Dr. Blair Smith claims that “since talcum powder and its causal relationship with ovarian cancer is compatible with our knowledge of cancer and cancer processes,” this consideration of the Bradford Hill criteria has been satisfied (p. 21). This is an unsubstantiated assertion. A scientist cannot just say that because a hypothesis makes theoretical sense, it is so. Instead, scientific data are needed to support the contention, and once again, no data are supplied in the report. Lastly, Dr. Wolf makes a big, unsupported leap when she states that the “most compelling disease associated with talcum powder use is epithelial ovarian cancer, therefore specificity for a disease is demonstrated” (p. 15). This is no more scientific than stating that since we do not actually know what causes ovarian cancer, we may as well blame talc. Under her logic, one could also presume that eating processed meat, watching television for >/ 5 hours per day and taking anti-anxiety medications are all causal in the development of ovarian cancer since there is epidemiological literature that has demonstrated statistically significant associations between these factors and the occurrence of ovarian cancer (68, 81,93). But an association (especially a modest one) is not determinative of a causal relationship, and talc is no more causal of ovarian cancer than watching television or taking Valium.

Conclusions

As a physician who has dedicated her career to the care of women who develop ovarian cancer, I hope that someday we will know what causes ovarian cancer. Knowing more about the cause of this deadly disease would allow us to take more effective measures to help reduce its incidence and mortality rate. This is in part what we have done by performing risk-reducing surgery on women who carry genetic mutations that predispose them to the development of the disease, which accounts for ~ 20-25% of ovarian cancer cases. But junk science will not help women at risk for cancer, and plaintiffs’ claim that talc causes ovarian cancer is simply not borne out by the data. As

explained in this report, there is inconsistency amongst the epidemiologic literature, and plaintiffs' theories with respect to migration and the mechanism by which talc might cause cancer through inflammation are nothing more than speculation, unsupported by sound science. Attributing a causal role to talc in the development of ovarian cancer will not help anybody because no cases of ovarian cancer will be prevented, and the incidence and mortality of the disease will not be reduced by false science.

References

1. **ACOG** *Frequently Asked Questions: Gynecologic Problems: Ovarian Cancer* (July 2017)
<https://www.acog.org/Patients/FAQs/Ovarian-Cancer#risk>
2. **Barnard ME.**, et al. Association of analgesic use with risk of ovarian cancer in the Nurses' Health Studies. *JAMA Oncology* 2018; 4(12), 1675-1682.
3. **Berge W.**, et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention* 2018; 27(3), 248-257.
4. **Booth M.**, et al. Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer* 1989; 60:592-8.
5. **Centers for Disease Control and Prevention** *What are the Risk Factors for Ovarian Cancer?* (Page last reviewed: February 9, 2017)
https://www.cdc.gov/cancer/ovarian/basic_info/risk_factors.htm
6. **Chang S.**, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. *Cancer* 1997; 79:2396-401.
7. **Chen Y.**, et al. Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology* 1992; 21(1), 23-29.
8. **Collaborative Group on Epidemiological Studies of Ovarian Cancer.** Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *The Lancet* 2008; 371(9609), 303-314.
9. **Collaborative Group on Epidemiological Studies of Ovarian Cancer.** Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *The Lancet* 2015; 385(9980), 1835-1842.
10. **Cook LA.**, et al. Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology* 1997; 145:459-65.
11. **Cramer DW.**, et al. Ovarian cancer and talc. A case-control study. *Cancer* 1982; 50(2), 372-376.
12. **Cramer DW.**, Huijuan, XU. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Annals of Epidemiology* 1995; 5(4), 310-314.

13. **Cramer DW.**, et al. Over-the-counter analgesics and risk of ovarian cancer. *The Lancet* 1998; 351(9096), 104-107.
14. **Cramer DW.**, Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstetrics & Gynecology* 1999; 94:160-1.
15. **Cramer DW.**, et al. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case control study in two US States. *Epidemiology* 2016; 27(3):334-346.
16. **Domcheck SM.**, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality 2010; *JAMA* 304(9):967-75.
17. **Egli GE.**, Newton M. The transport of carbon particles in the human female reproductive tract. *Fertility and Sterility* 1961; 12(2), 151-155.
18. **Eng K.**, et al. Paternal lineage early onset hereditary ovarian cancers: A Familial Ovarian Cancer Registry study. *PLOS Genetics* 2018; 14 (2): e1007194.
19. **Fathalla MF.** Incessant ovulation—a factor in ovarian neoplasia. *Lancet* 1971; 2(7716), 163.
20. **Food and Drug Administration** Letter from Musser SM to Epstein SS Re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP. Date stamped: April 1, 2014. April 1, 2014 FDA Denial of 1994 and 2008 Petitions
21. **Fletcher NM.**, et al. Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells. *Reproductive Sciences* 2018; 25:214A-215A
22. **Friedlander ML.** Prognostic factors in ovarian cancer. *Seminars in Oncology* 1998 Jun; 25(3):305-14.
23. **Gates MA.**, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2008; 17(9):2436-44.
24. **Gates MA.**, et al. Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype. *American Journal of Epidemiology* 2010; 171:45-53.
25. **Gertig DM.**, et al. Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute* 2000; 92:249-52.

26. **Godard B.**, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *American Journal of Obstetrics and Gynecology* 1998; 179(2), 403-410.
27. **Gonzalez N.**, et al. Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiology* 2016; 27(6):797-802.
28. **Goodman MT.**, et al. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. *Endocrine-related Cancer* 2008; 15(4), 1055-1060.
29. **Gray H.** The Organs of the Special Sense. The Eye. *In Gray's Anatomy The Classic Collector's Edition*. New York, Bounty Books, 1977. p. 826.
30. **Green A.**, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *International Journal of Cancer* 1997; 71(6), 948-951.
31. **Gross AJ.**, Berg PH., et al. A Meta-Analytical Approach Examining the Potential Relationship between Talc. *Journal of Exposure Analysis and Environmental Epidemiology* 1995; 5(2):181-195.
32. **Hall HI.**, et al. Second primary ovarian cancer among women diagnosed previously with cancer. *Cancer Epidemiology and Prevention Biomarkers* 2001; 10(9), 995-999.
33. **Harlow BL.**, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *American Journal of Epidemiology* 1989; 130(2), 390-394.
34. **Harlow BL.**, et al. Perineal exposure to talc and ovarian cancer risk. *Obstetrics & Gynecology* 1992; 80:19-26.
35. **Hartge P.**, et al. Talc and ovarian cancer. *JAMA* 1983; 250:1844.
36. **Heller DS.**, et al. Asbestos exposure and ovarian fiber burden. *American Journal of Industrial Medicine* 1996; 29:435-439.
37. **Heller DS.**, et al. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *American Journal of Obstetrics & Gynecology* 1996; 174:1507-10.
38. **Houghton SC.**, et al. Perineal Powder Use and Risk of Ovarian Cancer. *Journal of the National Cancer Institute* 2014; 106(90), 208.

39. **Huncharek**, et al. Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from 16 Observational Studies. *Anticancer Research* 2003; 23:955-1960.
40. **International Agency for Research on Cancer**. *IARC monographs on the evaluation of carcinogenic risks to humans, Vol 93. Carbon Black, Titanium Dioxide, and Talc*. Lyon: World Health Organization, 2010.
41. **International Agency for Research on Cancer**. *IARC monographs on the evaluation of carcinogenic risks to humans, Vol 100C. Arsenic, Metals, Fibres and Dusts*. Lyon: World Health Organization, 2012.
42. **Jordan SJ.**, et al. Does smoking increase risk of ovarian cancer? A systematic review. *Gynecologic Oncology* 2006; 103(3), 1122-1129.
43. **Jordan SJ.**, et al. Risk factors for benign serous and mucinous epithelial ovarian tumors. *Obstetrics & Gynecology* 2007; 109:647-54.
44. **Jordan SJ.**, et al. Breastfeeding and risk of epithelial ovarian cancer. *Cancer Causes & Control* 2010; 21(1), 109-116.
45. **Kazerouni N.**, et al. Family history of breast cancer as a risk factor for ovarian cancer in a prospective study. *Cancer: Interdisciplinary International Journal of the American Cancer Society* 2006; 107(5), 1075-1083.
46. **Kurta ML.**, et al. Use of fertility drugs and risk of ovarian cancer: Results from a US-based case-control study. *Cancer Epidemiology and Prevention Biomarkers* 2012; 21(8), 1282-1292.
47. **Langseth H.**, et al. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *International Journal of Gynecological Cancer* 2007; 17(1), 44-49.
48. **Langseth H.**, et al. Perineal use of talc and risk of ovarian cancer. *Journal of Epidemiology and Community Health* 2008; 62(4):358-360.
49. **Li DP.**, et al. Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. *Asian Pacific Journal of Cancer Prevention* 2014; 15(12), 4829-4837.
50. **Liu Z.**, et al. The association between overweight, obesity and ovarian cancer: a meta-analysis. *Japanese Journal of Clinical Oncology* 2015; 45(12):1107-15.
51. **Lo-Cigancic WH.**, et al. Aspirin, Non-Aspirin Nonsteroidal Anti-inflammatory Drugs, or Acetaminophen and risk of ovarian cancer. *Epidemiology* 2012; 23(2), 311-319.

52. **Merritt MA.**, et al. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer* 2008; 122(1), 170-176.
53. **Mills PK.**, et al. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *International Journal of Cancer* 2004; 112, 458-64.
54. **Moorman PG.**, et al. Ovarian cancer risk factors in African-American and white women. *American Journal of Epidemiology* 2009; 170(5), 598-606.
55. **Narod S.**, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *New England Journal of Medicine* 1998; 339(7):424-8.
56. **National Cancer Institute** *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated January 4, 2019)
https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11
57. **National Cancer Institute, Surveillance, Epidemiology and End Results Program:** *Cancer Stat Facts: Ovarian Cancer* (last accessed February 14, 2019)
<https://seer.cancer.gov/statfacts/html/ovary.html>
58. **National Cancer Institute, SEER Training Modules:** *Ovarian, Fallopian Tube, and Primary Peritoneal Cancers: Risk Factors* (updated June 8, 2018)
<https://training.seer.cancer.gov/ovarian/intro/risk.html>
59. **Ness RB.**, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* 2000; 11:111-7.
60. **Olsen CM.**, et al. Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium. *Endocrine-Related Cancer* 2013; 20(2), 251-262.
61. **Ovarian Cancer Research Alliance** *Risk Factors* (last accessed January 24, 2019)
<https://ocrahope.org/patients/about-ovarian-cancer/risk-factors/>
62. **Penninkilampi R.**, et al. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology* 2018; 29(1), 41-49.
63. **Pike MC.**, et al. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertility and Sterility* 2004; 82(1), 186-195.

64. **Purdie D.**, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *International Journal of Cancer* 1995; 62:678-84
65. **Ramus SJ.**, Gayther, SA. The contribution of BRCA1 and BRCA2 to ovarian cancer. *Molecular Oncology* 2009; 3(2), 138-150.
66. **Rasmussen CB.**, et al. Pelvic inflammatory disease and the risk of ovarian cancer and borderline ovarian tumors: a pooled analysis of 13 case-control studies. *American Journal of Epidemiology* 2017; 185(1), 8-20.
67. **Roman A.**, et al. The papillomavirus E7 proteins. *Virology*. 2013; 445:138-168.
68. **Rosato V.**, et al. Processed meat and selected hormone-related cancers. *Nutrition* 2018; 49:17-23.
69. **Rosenblatt KA.**, et al. Mineral fiber exposure and the development of ovarian cancer. *Gynecologic Oncology* 1992; 45:20-5.
70. **Rosenblatt KA.**, et al. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control* 2011; 22(5), 737-742.
71. **Sainz de la Cuesta RS.**, et al. Histologic transformation of benign endometriosis to early epithelial ovarian cancer. *Gynecologic Oncology* 1996; 60(2), 238-244.
72. **Schildkraut JM.**, et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers* 2016; cebp-1281.
73. **Sedlis A.**, Robboy SJ. Diseases of the vagina. In: Kurman RJ, editor. *Blaustein's Pathology of the Female Genital Tract*. 3rd ed. New York: Springer-Verlag; 1989. p 98-103.
74. **Shushan A.**, et al. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertility and Sterility* 1996; 65(1), 13-18.
75. **Sieh W.**, et al. Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. *International Journal of Epidemiology* 2013; 42(2), 579-589.
76. **Society of Gynecologic Oncology** *Ovarian Cancer: Risk Factors* (last accessed January 24, 2019)
<https://www.sgo.org/patients-caregivers-survivors/caregivers/ovarian-cancer-risk-factors/>

77. **Sutcliffe S.**, et al. Familial Ovarian Cancer Study Group. Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. *International Journal of Cancer* 2000; 87(1), 110-117.
78. **Taşkın S.**, et al. Malignant peritoneal mesothelioma presented as peritoneal adenocarcinoma or primary ovarian cancer: case series and review of the clinical and immunohistochemical features. *International Journal of Clinical and Experimental Pathology* 2012; 5(5), 472-478.
79. **Terry KL.**, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research* 2013;DOI:10.1158/1940-6207.CAPR-13-0037.
80. **Tzonou A.**, et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *International Journal of Cancer* 1993; 55:408-10.
81. **Ukawa S.**, et al. Association between average daily television viewing time and the incidence of ovarian cancer: findings from the Japan Collaborative Cohort Study. *Cancer Causes & Control* 2018; 29(2), 213-219.
82. **Vande Pol SB.**, et al. Papillomavirus E6 oncoproteins. *Virology*. 2013; 445:115-137.
83. **Venn A.**, et al. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet* 1995; 346:995-1000.
84. **Venter M.** Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *South African Medical Journal* 1979; 55(23), 917-919.
85. **Walsh T.**, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proceedings of the National Academy of Sciences USA* 2011; 108(44):18032-7.
86. **Webb P** et al. Epidemiology of epithelial ovarian cancer. *Best Practice & Research: Clinical Obstetrics & Gynecology* 2017; 41:3-14.
87. **Wentzensen N.**, et al. Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. *Journal of Clinical Oncology* 2016; 34(24), 2888-2898.
88. **Whittemore AS.**, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology* 1988; 128:1228-40.

89. **Whittemore AS.**, et al. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies: IV. Pathogenesis of epithelial ovarian cancer. *American Journal of Epidemiology* 1992; 136(10), 1212-1220.
90. **Wong C.**, et al. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstetrics & Gynecology* 1999; 93:372-6.
91. **Wu AH.**, et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County *International Journal of Cancer* 2009; 124:1409-1415.
92. **Wu AH.**, et al. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. *Cancer Epidemiology, Biomarkers & Prevention* 2015; Apr 14: DOI: 10.1158/1055-9965.EPI-15-0023.
93. **Zhang T.**, et al. Benzodiazepine drug use and cancer risk: a dose–response meta-analysis of prospective cohort studies. *Oncotarget* 2017; 8(60), 102381.

Additional Materials Reviewed by Dr. Cheryl Saenz:

Expert Reports:

- Expert Report of Arch Carson, M.D. (filed Nov. 16, 2018)
- Expert Report of Daniel L. Clarke-Pearson, M.D. (filed Nov. 16, 2018)
- Expert Report of Ellen Blair Smith, M.D. (filed Nov. 16, 2018)
- Expert Report of Ghassan Saed, PhD (filed Nov. 16, 2018)
- Expert Report of Judith Wolf, M.D. (filed Nov. 16, 2018)
- Expert Report of Rebecca Smith-Bindman, M.D. (filed Nov. 15, 2018)
- Expert Report of Shawn Levy, PhD (filed Nov. 16, 2018)

Deposition Transcripts:

- January 7, 2019 Deposition transcript of Judith K. Wolf, M.D.
- January 9, 2019 Deposition transcript of Ellen Blair Smith, M.D.
- January 4, 2019 Deposition transcript of Michael Crowley, PhD
- January 11, 2019 Deposition transcript of Shawn Levy, PhD
- January 19, 2019 Deposition transcript of Arch Carson, M.D.
- January 23, 2019 Deposition transcript of Ghassan Saed, PhD
- February 4, 2019 Deposition transcript of Daniel L. Clarke-Pearson, M.D.
- February 7 & 8, 2019 (Vol. I & II) Deposition transcript of Rebecca Smith-Bindman, M.D.
- February 14, 2019 Deposition transcript of Ghassan Saed, PhD and Ex. 35

Literature:

1. **Aylott RI.**, et al. Normal use levels of respirable cosmetic talc: preliminary study. *International J of Cosmetic Science* 1979; 1:177-186.
2. **Camargo M.**, et al Occupational Exposure to Asbestos and Ovarian Cancer - Meta-analysis. *Environmental Health Perspectives* 2011; 119(9), 1211-1217.

3. **Carr CJ.** Talc: Consumer Uses and Health Perspectives. *Reg Toxicol Pharmacol* 1995; 21:211-215.
4. **Craig E., et al.** Metabolic risk factors and mechanisms of disease in epithelial ovarian cancer: A review. *Gynecol Oncol* 2016; 143(3):674-683.
5. **Crawford, et al.** Perineal powder use and risk of endometrial cancer in postmenopausal women. *Cancer Causes Control* 2012; 23(10), 1673-1680.
6. **Fiume MM., et al.** Safety Assessment of Talc as Used in Cosmetics. *Int J Toxicol.* 2015; 34(1 Suppl):66S-129S.
7. **Food and Drug Administration,** Statement on Talc (2015).
8. **Harlow BL** and Hartge PA. A review of perineal talc exposure and risk of ovarian cancer. *Regul Toxicol Pharmacol* 1995; 21:254-60.
9. **Health Canada** *Health Canada Decision –Making Framework for Identifying, Assessing, and Managing Health Risks* (August 1, 2000).
10. **Health Canada** *Draft Screening Assessment: Talc ($Mg_3H_2(SiO_3)_4$), Chemical Abstracts Service Registry Number 14807-96-6* (December 2018).
11. **Heller DS., et al.** Presence of asbestos in peritoneal malignant mesotheliomas in women. *Int J Gynecol Cancer* 1999; 9:452-455.
12. **Heller DS, et al.** Correlation of asbestos fiber burdens in fallopian tubes and ovarian tissue. *An J Obstet Gynecol* 1999; 181(2), 346-347.
13. **Karageorgi, et al.** Perineal use of talcum powder and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2010; 1055-9965.
14. **Kotsopoulos, et al.** Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin. *Int J Cancer* 2013; 133(3):730-740.
15. **Muscat JE** and Huncharek MS. Perineal talc use and ovarian cancer: a critical review. *Eur J Cancer Prev* 2008; 17:139-46.
16. **National Cancer Institute (NCI).** *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ)*, April 2017.
17. **National Cancer Institute,** *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ)*, February 2016.

18. **Neill**, et al. Use of talcum powder and endometrial cancer risk. *Cancer Causes Control* 2012; 23:513-519.
19. **Ness R**. Does talc exposure cause ovarian cancer? IGCS-0015 Ovarian Cancer. *Int J Gynecol Cancer* 2015; 25(Suppl 1):51.
20. **Olsen CM.**, et al. Comparison of symptoms and presentation of women with benign, low malignant potential and invasive ovarian tumors. *Eur J Gynaecol Oncol*. 2007; 28(5):376-80.
21. **Peres LC.**, et al. Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies. *International Journal of Epidemiology* 2017; 1–13.
22. **Reid A.**, et al. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis; *Cancer Epidemiol Biomarkers Prev* 2011; 20(7); 1287-95.
23. **Stanton MF.**, et al. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *Journal of the National Cancer Institute* 1981; 67(5), 965-975.
24. **Taher MK**, e.t al. Systematic Review and Meta-Analysis of the Association between Perineal Use of Talc and Risk of Ovarian Cancer. Health Canada (Unpub).

Table 1: Analysis of Case Control Studies Cited by Dr. Smith-Bindman in Table 4 of her Expert Report

	OR/RR for ever/never genital only	SS or NS	Mistakes in reported data in Table 4 of Smith-Bindman's report
Schildkraut 2016	1.44 (1.11,1.86)	SS	incorrect OR
Cramer 2016*	1.33 (1.16,1.52)	SS	incorrect OR
Wu 2015	1.46 (1.27,1.69)	SS	no mistakes
Kurta 2012	1.40 (1.16,1.69)	SS	incorrect OR
Lo-Cignaia 2012**	1.34 (1.07-1.67)	SS	incorrect CI only
Rosenblatt 2011	1.27 (0.97,1.66)	NS	incorrect OR
Wu 2009	1.53 (1.13,2.09)	SS	incorrect OR
Moorman 2009	1.04 (0.82,1.33) (Cau)	NS	incorrect OR and claims SS
	1.19 (0.68,2.09) (AA)	NS	not reported
Merritt 2008	1.17 (1.01,1.36)	SS	incorrect OR
Gates 2008	1.36 (1.14,1.63)	SS	incorrect OR
Goodman 2008**	0.99 (0.7,1.41)	NS	no mistakes
Pike 2004	1.60 (1.18,2.18)	SS	missing OR
Mills 2004	1.37 (1.02,1.85)	SS	incorrect OR
Ness 2000	1.5 (1.1,2.0)	SS	no mistakes
Cramer 1999	1.6 (1.18,2.15)	SS	no mistakes
Wong 1999	1.1 (0.7,1.7)	NS	incorrect OR
Godard 1998	2.49 (0.94,6.58)	NS	incorrect CI only
Green 1997	1.30 (1.10,1.60)	SS	mistates year of publication only
Cook 1997	1.6 (0.9,2.80)	NS	incorrect CI only
Chang 1997	1.42 (1.08,1.86)	SS	incorrect OR
Purdie 1995	1.27 (1.04,1.54)	SS	no mistakes
Tzonou 1993	1.05 (0.28,3.98)	NS	no mistakes
Harlow 1992	1.5 (1.0,2.1)	NS	incorrect OR and claims SS
Rosenblatt 1992	1.70 (0.70,3.90)	NS	no mistakes
Chen 1992	3.90 (0.90,10.63)	NS	no mistakes
Booth 1989	1.30 (0.8,1.90)	NS	no mistakes
Harlow 1989	1.10 (0.70,2.10)	NS	no mistakes
Whittemore 1988	1.45 (0.81,2.60)	NS	incorrect CI only
Hartge 1983	2.5 (0.7,10.0)	NS	no mistakes
Cramer 1982	1.92 (1.27,2.89)	SS	incorrect OR and claims NS

* Included as a case control study, consistent with publication title, but notably contains data set from Cramer 1999.

**As reported in Terry 2013 pooled analysis

NB: Case-control studies that are "grayed out" above have been withdrawn from the analysis in this report as the data has been subsumed into later case-control studies. (Purdie 1995 in Green 1997; Cramer 1999 in Cramer 2016; Pike 2004 and Wu 2009 in Wu 2015).

Excluded Shushan 1996 from chart as that study did not provide confidence intervals.

Table 2: Overlap of Case-Control Studies Cited in Systematic Review Articles

	Penninkilampi (2018) n=24	Berge (2018) n=24	Terry (2013) n=8	Langseth (2008) n=20	Huncharek (2003) n=15	Cramer (1999) n=14	Gross and Berg (1995) n=9	Harlow (1992) n=6
Cramer et al (1982)	✗	✓	✗	✓	✓	✓	✓	✓
Hartge et al (1983)	✓	✓	✗	✓	✗	✓	✓	✓
Whittemore et al (1988)	✓	✓	✗	✓	✓	✓	✓	✓
Booth et al (1989)	✓	✓	✗	✓	✓	✓	✓	✓
Harlow & Weiss (1989)	✓	✓	✗	✓	✓	✓	✓	✓
Harlow et al (1992)	✗	✓	✗	✓	✓	✓	✓	✓
Chen et al (1992)	✓	✓	✗	✓	✓	✓	✓	✗
Rosenblatt et al (1992)	✓	✓	✗	✓	✓	✓	✓	✗
Tzonou et al (1993)	✓	✓	✗	✓	✓	✓	✓	✗
Purdie et al (1995)	✓	✓	✗	✓	✓	✓	✗	✗
Cramer et al (1995)	✓	✗	✗	✓	✗	✗	✗	✗
Shushan et al (1996)	✓	✗	✗	✗	✗	✓	✗	✗

Chang & Risch (1997)	✓	✓	✓	✓	✓	✓	×	×
Cook et al (1997)	✓	✓	×	✓	✓	✓	×	×
Green et al (1997)	✓	×	×	✓	×	×	×	×
Godard et al (1998)	✓	✓	×	✓	✓	×	×	×
Cramer (1999)	×	×	✓	✓	✓	✓	×	×
Wong et al (1999)	✓	✓	×	✓	✓	×	×	×
Ness et al (2000)	✓	✓	×	✓	✓	×	×	×
Mills et al (2004)	✓	✓	×	✓	×	×	×	×
Pike et al (2004)	×	×	✓	×	×	×	×	×
Jordan et al (2007)	×	×	×	✓	×	×	×	×
Goodman et al (2008)	×	✓	✓	×	×	×	×	×
Merritt et al (2008)	✓	✓	✓	×	×	×	×	×
Moorman et al (2009)	×	✓	✓	×	×	×	×	×
Wu et al (2009)	✓	×	×	×	×	×	×	×
Rosenblatt et al (2011)	✓	✓	✓	×	×	×	×	×
Kurta et al	✓	×	×	×	×	×	×	×

(2012)								
Lo-Ciganic et al (2012)	×	✓	✓	×	×	×	×	×
Wu et al (2015)	✓	✓	×	×	×	×	×	×
Cramer et al (2016)	✓	✓	×	×	×	×	×	×
Schildkraut et al (2016)	✓	✓	×	×	×	×	×	×

EXHIBIT A



UNIVERSITY of CALIFORNIA, SAN DIEGO
MEDICAL CENTER MOORES CANCER CENTER

CURRICULUM VITAE

PERSONAL

NAME: Cheryl Christine Saenz, M.D.

MAIDEN NAME: Cheryl Christine Gurin, M.D.

POSITION: Clinical Professor
University of California, San Diego
School of Medicine

BUSINESS ADDRESS: Moores UCSD Cancer Center
Division of Gynecologic Oncology
3855 Health Sciences Drive Mail Code: 0987
La Jolla, CA 92093-0987

Academic Office: (858) 822-6275
Case Manager: (858) 822-5417
Fax: (858) 822-6319
Email: csaenz@ucsd.edu

DATE OF BIRTH August 1961

EDUCATION

COLLEGE: Cornell University
College of Arts and Sciences
Ithaca, NY
B.A. 1985
Biopsychology

MEDICAL SCHOOL: University of California, Irvine
College of Medicine
Irvine, CA
M.D. 1991

Moore's UCSD Cancer Center

3855 Health Science Drive, Mail Code 0987, La Jolla, California 92093-0987 TEL (858) 822-6275 FAX (858) 822-6319

POSTDOCTORAL TRAINING

Resident in Reproductive Medicine
University of California Medical Center
San Diego, CA
1991-1995

Galloway Fellow
Memorial Sloan-Kettering Cancer Center
New York, NY
1993

Fellow in Gynecologic Oncology
Memorial Sloan-Kettering Cancer Center
New York, NY
1995-1998

Junior Faculty Mentoring Fellowship
National Center for Leadership in Academic Medicine
University of California, San Diego
San Diego, CA
2001

Women's Reproductive Health Research Scholars Program
Principal Investigator: Thomas R. Moore, M.D.
Mentor: Steven F. Dowdy, Ph.D.
Departments of Reproductive Medicine and Cellular and Molecular
Medicine
University of California, San Diego
Agency: NIH HD-99-001
Research Career Development Center in Reproductive Sciences
Fellow, September 2002 – February 2007

Physician Leadership Academy
University of California, San Diego
San Diego, CA
2007 – 2009

Mid-Career Women Faculty
Professional Development Seminar
Association of American Medical Colleges/Harvard Medical School
Scottsdale, AZ
December 2008

CERTIFICATION

American Board of Obstetrics and Gynecology – 1999
Recertification 2016
Subspecialty of Gynecologic Oncology – 2001
Recertification 2016
Certificate #: 950475

LICENSING

California - GO74647 (1992)
New York - 199704 (Inactive)
U.S. Drug Enforcement Administration - BG3305100

ACADEMIC APPOINTMENTS

Assistant Clinical Professor
Division of Gynecologic Oncology
Department of Reproductive Medicine
University of California, San Diego School of Medicine
October 1998 – June 2004

Associate Clinical Professor
Division of Gynecologic Oncology
Department of Reproductive Medicine
University of California, San Diego School of Medicine
July 2004 – June 2010

Clinical Professor
Division of Gynecologic Oncology
Department of Reproductive Medicine
University of California, San Diego School of Medicine
July 2010 – Present

ADMINISTRATIVE APPOINTMENTS

Director for Ambulatory Access
UCSD Medical Group
University of California, San Diego School of Medicine
August 2007 – July 2012

Medical Director
Strauss Family Center for the Early Detection of Ovarian Cancer
July 2010 - Present

SCIENTIFIC AND MEDICAL SOCIETIES

1995 – Present	Fellow American Congress of Obstetrics and Gynecology
1999 - Present	Diplomat American Board of Obstetrics and Gynecology
1998 - Present	Full Member Society of Gynecologic Oncology
2001 – Present	Fellow American College of Surgeons
2001 - Present	Full Member Western Association of Gynecologic Oncologists
2006 – Present	Full Member American Association for Cancer Research
2006 – Present	Full Member American Society of Clinical Oncology

SCHOOL OF HEALTH SCIENCES COMMITTEES

1999 – 2012	Member, Cancer Committee University of California, San Diego Medical Center
2001 – 2012	Chair, Cancer Committee University of California, San Diego Medical Center
2002 – 2016	Co-Leader, Gynecologic Oncology Specialized Cancer Units Moores UCSD Cancer Center
2005 – 2009	Member, Service Excellence Committee Moores UCSD Cancer Center
2006 – 2008	Subcommittee Leader, Programs of Excellence Strategic Planning Committee Moores UCSD Cancer Center
2007 – Present	Member, Academy of Clinical Scholars UCSD School of Medicine

2007 – 2012	Member, Board of Governors University of California, San Diego Medical Center
2007 – 2012	Member, Cancer Center Cabinet Moore's UCSD Cancer Center
2007 – 2012	Member, Medical Group Operations Committee University of California, San Diego Medical Group
2007 – 2012	Member, Professional Standards Committee University of California, San Diego Medical Group
2010 – 2012	Member, Dean's Executive Council Faculty Development Committee UCSD School of Health Sciences
2011 – 2012	Chair, Professional Standards Committee University of California, Medical Group
2013	Member, Five-year Review Committee for Reappointment of Chair of the Department of Anesthesiology
2014 – 2017	Member-At-Large Health Sciences Faculty Council
2014 – Present	Member Health Sciences Faculty Equity Committee

PROFESSIONAL SOCIETY COMMITTEE APPOINTMENTS

Member, Coding Taskforce
Society of Gynecologic Oncology
2019-present

Member, Media Response Team
Foundation for Women's Cancer
2002-2016

Member, Marketing and Communications Committee
Society of Gynecologic Oncology
2004-2013

Board of Directors

Foundation for Women's Cancer
2007 – 2013

Member, Cervix and Vulvar Cancer Committee
Gynecologic Oncology Group
2009-2012
Co-Chair, Education Committee
Foundation for Women's Cancer
2009-2012

Member, 2010 Program Committee
Western Association of Gynecologic Oncologists
Annual Meeting on Gynecologic Cancers
2009-2010

Chair, Media Relations Subcommittee
Marketing and Communications Committee
Society of Gynecologic Oncology
2010-2012

Member, 2011 Program Committee
Society of Gynecologic Oncology
Annual Meeting on Women's Cancer
2010-2011

Chair, Education Committee
Foundation for Women's Cancer
2012-2016

Member, Society of Gynecologic Oncology
2013 Nominating Committee

AD HOC REVIEWER

Gynecologic Oncology
American Journal of Obstetrics and Gynecology
Cancer
Journal of Pediatric Surgery Case Reports

HONORS AND ACTIVITIES

Content Expert, Analysis of Assembly Bill 547
Ovarian Cancer Screening
California Health Benefits Review Program
A Report to the 2003-2004 California Legislature

Course Director, Ovarian Cancer Survivors' Course
Moores UCSD Cancer Center/Gynecologic Cancer Foundation
January 2006

Walter T. Danreuther Award
The American Association of Obstetricians and Gynecologists Foundation
September 2006

Interim Director, Infusion Center
Moores Cancer Center
UC San Diego Health System
2006–2007

Women's Reproductive Health Research Scholars Program
Member, Internal Advisory Board
2007-2016

Leader, Internal Task Force
Comprehensive Patient Safety Audit
Moores UCSD Cancer Center Infusion Center
April 2007

Content Expert, Analysis of Assembly Bill 1774
Coverage for Gynecologic Cancer Screening Tests
California Health Benefits Review Program
A Report to the 2007-2008 California Legislature

Course Director, Cancer Biology
Young Women in Cancer Research Oncofertility Academy
Better Education for Women in Science and Engineering Program
2008-2016

Course Director, Gynecologic Cancer Wellness Symposium
'From Tai Chi to Chai Tea – What You Can Do to Promote Gynecologic
Health', Supported by the Web MD Foundation and the Gynecologic
Cancer Foundation, Moores UCSD Cancer Center
January 2010

HOSPITAL APPOINTMENTS

Attending Surgeon
UC San Diego Health System– San Diego, CA
10/98 – Present

Attending Physician
Scripps Memorial Hospital – San Diego, CA
1/99 – 2011

Attending Physician
Rady Children's Hospital - San Diego, CA
10/99 - 2012

Attending Physician
Palomar/Pomerado Health Care System
11/99 - 2010

SELECTED LECTURESHIPS AND PRESENTATIONS

“Ten-year Trends in Pre-invasive and Invasive Cervical Neoplasia in Southern California”, Western Association of Gynecologic Oncologists, 1995.

“Pathological Risk Factors and Outcomes for Isolated Adnexal Metastases in Endometrial Cancer”, Society of Memorial Gynecologic Oncologists, 1996.

“Clinicopathologic Features of Endometrial Cancer Occurring in Patients with a Family History Suspicious for Hereditary Nonpolyposis Colorectal Cancer”, Society of Gynecologic Oncologists, 1998.

“Fertility Agents and the Risk of Ovarian Cancer”, Grand Rounds, Department of Reproductive Medicine, University of California, San Diego, 1999.

“The Use of Operative Laparoscopy in Gynecologic Oncology”, A Gynecologic Oncology Update Seminar, San Diego, CA, 1999.

“Fertility Agents and the Risk of Ovarian Cancer”, San Diego Gynecologic Society, San Diego, CA, 1999.

"Ovarian Cancer" Lecture Hematology/Oncology Fellows, Veterans Administrative Hospital, San Diego, CA, 2000.

"Gynecologic Cancer Screening in the Year 2000", UCSD Cancer Center Associates Meeting, San Diego, CA, 2000.

"Abnormal Pap Smears", Advances in Urology and Gynecology for Primary Care Seminar, San Diego, CA, 2000.

"Advances in Gynecologic Cancer Treatment", The Wellness Community, San Diego, CA, 2000.

"Gynecologic Oncology Cancer Survivorship", Cancer Survivorship Seminar, San Diego, CA, 2000.

"Screening Your Patient Over 40 for Gynecologic Malignancies", Current Trends in Women's Health Seminar, San Diego, CA, 2000.

"Abnormal Pap Smears", Advances in Urology and Gynecology for Primary Care Seminar, San Diego, CA, 2001.

"Update in Gynecologic Cancers", Advances in Urology and Gynecology for Primary Care Seminar, San Diego, CA, 2002.

"Treatment of Terminal Peritoneal Carcinomatosis by a Transducible p53-Activating Peptide", Grand Rounds, Department of Reproductive Medicine, University of California San Diego, 2004.

"Selective Targeting and Killing of Tumor Cells Expressing Tumor-Associated Receptors by Transducible Anti-Cancer Peptides", Women's Reproductive Health Research Scholars' Symposium, Cincinnati, OH 2005.

"HPV and the Abnormal Pap Smear – What We've Learned in the Last Five Years", Primary Care Grand Rounds, Departments of Reproductive Medicine and Family Medicine, University of California San Diego, 2006.

"Selective Targeting and Killing of Tumor Cells Expressing Tumor-Associated Receptors by Transducible Anti-Cancer Peptides", American Gynecologic Club Annual Meeting, La Jolla, CA, 2006.

"Ovarian Cancer – What You Need to Know", Faculty Ambassador Event, Moores UCSD Cancer Center, La Jolla, CA 2007.

"HPV and Cervical Cancer: Current Screening Guidelines", Sidney Kimmel Cancer Center Seminar, La Jolla, CA, 2008.

"Surgical Management of the Placenta Accreta", 5th Annual Perinatology Symposium, Department of Reproductive Medicine, University of California, San Diego, 2008.

“Chemotherapy in Cancer,” Young Women in Cancer Research Saturday Academy, Oncofertility Consortium, Moores UCSD Cancer Center, University of California, San Diego, 2008.

“What Can I Do if I’m at Risk for Ovarian Cancer”, Management of the High Risk Patient, Ovarian Cancer Community Outreach Symposium, Moores UCSD Cancer Center, La Jolla CA, 2008.

“Family History, Genetic Risk and Ovarian Cancer”
Ovarian Cancer Survivors Courses, Gynecologic Cancer Foundation, San Antonio, Texas, 2009, Phoenix AZ, 2009, Las Vegas, NV, 2009, Richmond VA, 2010, Washington D.C., 2011, Austin TX 2012, Las Vegas, 2013.

“The Hereditary Component of Ovarian Cancer”
Women’s Wellness Day
UC San Diego Health System, La Jolla CA, 2013.

“The Hereditary Component of Ovarian Cancer”
Society of Gynecologic Nurse Oncologists
31st Annual Symposium
April 2013, San Diego, CA

“The Invasive Placenta – A Multidisciplinary Team Approach Utilizing Balloon Catheters”
2015 Annual Meeting on Women’s Cancer
Postgraduate Course Lecture
March 2015, Chicago, IL

RESEARCH SUPPORT

Completed Research Support

“Creating an Early Detection Test for Ovarian Cancer”

Principal Investigator: Christian Barrett

Co-Principal Investigator: Cheryl Saenz

Agency: Strauss Center for the Early Detection of Ovarian Cancer

Pilot Project Award

Period January 2014-December 2015

This study seeks to identify ovarian cancer in its earliest stages through the detection of RNA isoforms unique to ovarian cancer cells in cells collected from Pap smears.

“Translational Cancer Genomics: Application of the novel Network-based Stratification Technique to identify clinically relevant prognostic information from tumor somatic mutation profiles”

Principal Investigator: Trey Ideker

Co- Principal Investigators: Cheryl Saenz, Stephen Howell
Agency: UC San Diego Moores Cancer Center Translational and Clinical
Pilot Project Award
Period: May 2013-April 2014

This project will utilize a recently developed novel way of analyzing the information gained from genomic analyses of ovarian cancers that allows us to ‘cluster’ the mutations found in a manner that can predict response to chemotherapy as well as prognosis. As the cost of sequencing whole genomes or exomes remains quite high, in order to make this analysis more clinically useful, we seek to identify smaller sets of these ‘predictive mutations’ that could be then used cost effectively in the clinics to guide treatment options and decisions.

1R21CA162718-01

National Institutes of Health (NCI) \$500,000

PI: Loren Mell

Co-PI: Cheryl C. Saenz

Period: October 2011-September 2014

Image-guided bone marrow-sparing IMRT for cervical cancer

Major Goals: To estimate rates of acute hematologic toxicity associated with image-guided functional bone marrow-sparing intensity modulated radiation therapy in an international dual-center clinical trial

Clinical Investigator Team Leadership Award

Supplement to Specialized Cancer Center Support Grant

Agency: NCI 5P30CA23100-26

Period September 2010-August 2012

The support provided by this award is intended to allow the investigator to expand leadership responsibilities in investigator-initiated and Cooperative Group trials, increase accrual to clinical trials and continue to develop relationships with basic science researchers that allow for the bridging between basic science and clinical studies.

Women’s Reproductive Health Research Scholars Program

Principal Investigator: Thomas R. Moore

Agency: NIH HD-99-001

Type: K12HD01259-04

Research Career Development Center in Reproductive Sciences

Period: September 2002-February 2007

The major goal of this project is to provide protected time and salary support for 3-5 years to junior academic faculty in a mentor-based environment that will foster the development of clinician-scientists in translational research in women’s health.

“Role of Cytoplasmic P27^{KIP1} in Cell Motility and Metastasis”

Principal Investigator: Cheryl C. Saenz

Mentor: Steven F. Dowdy

Agency: Rebecca and John Moores UCSD Cancer Center Mentored
Translational Research Award

Period: December 2005-November 2006

This project aims to study the role of p27^{KIP1} in cell motility and the
relevance of its cytoplasmic localization in the development of tumor
invasion and metastasis.

“Transducible Therapeutic TAT-siRNAs: Treatment of Terminal Metastatic
Ovarian Cancer”

Principal Investigator: Cheryl C. Saenz

Co- Principal Investigator: Steven F. Dowdy

Agency: Rebecca and John Moores UCSD Cancer Center Collaborative
Translational Research Award

Period: August 2004-July 2005

This project aims to combine protein transduction with the specificity of
RNAi, to specifically kill tumor cells in terminal metastatic ovarian
peritoneal carcinomatosis mouse models by targeting genes that allow these
tumor cells to survive.

“Targeting of p53-activating Peptide to CXCR4 Receptor on Cancer Cells to
Enhance Anti-tumor Efficacy”

Principal Investigator: Cheryl C. Saenz

Agency: UCSD Academic Senate

Period: July 2004-June 2005

The goal of this project is to enhance the delivery of anti-cancer peptides to
tumor cells expressing specific receptors by linking the peptides to ligands
that bind these receptors.

“Treatment of Terminal Metastatic Ovarian Carcinoma by Transducible
Therapeutic siRNAs”

Principal Investigator: Cheryl C. Saenz

Agency: The Gynecologic Cancer Foundation/Florence and Marshall
Schwid Ovarian Cancer Grant

Period: January 2004-December 2004

The goal of this project is to combine two recent technological advances, *in
vivo* protein transduction delivery with the specificity of RNAi, to
specifically kill tumor cells in ovarian peritoneal mouse models by silencing
the genes that allow these tumors to escape apoptosis.

“Evaluation of Endometrial Stripe Thickness in Women with Endometrial
Cancer”

Principal Investigator: Cheryl C. Saenz

Agency: UCSD Academic Senate

Period: January 2001-December 2002

The goal of this project was to determine the thickness of the endometrial
stripe as measured by transvaginal ultrasound in women diagnosed with
endometrial cancer.

ABSTRACTS

Gurin CC, Plaxe SC: Ten-year trends in pre-invasive and invasive cervical neoplasia in Southern California. *Gynecol Oncol* 58:409-410, 1995.

Gurin CC, Hann L, Venkatraman E, Curtin JP, Barakat RR: Correlation of uterine surgical pathology with preoperative ultrasound measurement of endometrial stripe thickness. *Gynecol Oncol* 64:2, 1997.

Gurin CC, Blank S, Venkatratman E, Mychalczak B, Curtin JP, Barakat RR: Pathologic risk factors and outcomes for isolated adnexal metastases in endometrial cancer. *Gynecol Oncol* 64:2, 1997.

Gurin CC, Krygier A, Barakat RR: The practice of ovarian conservation in premenopausal endometrial cancer patients: A survey of the membership of the SGO. *Gynecol Oncol* 68:1, 1998.

Blank SV, **Gurin CC**, Barakat RR: Clinicopathologic features of endometrial cancer occurring in patients with a family history suspicious for hereditary nonpolyposis colorectal cancer. *Gynecol Oncol* 68:1, 1998.

Gurin CC, Federici MG, Kang L, Boyd J: Causes and consequences of microsatellite instability in endometrial carcinoma. *Gynecol Oncol*, 72:32, 1999.

Daly TL, Rock CL, Moskowitz A, Pidding A, **Saenz CC**, Behling C: Carotenoid-rich diet intervention for women diagnosed with cervical intraepithelial neoplasia. *J Amer Dietetic Assoc*, A-91, 2000.

Saenz CC, Snyder EL, Meade BR, Dowdy SF: Treatment of peritoneal carcinomatosis by a transducible p53-activating peptide. *Society of Gynecol Oncol*, Feb 2004.

Hanley A, **Saenz CC**, Madlensky L: Racial disparities in the time to treatment of cervical cancer among Hispanic women. *Western Assoc of Gynecol Oncol*, June 2008.

Saenz CC, Haripotepornkul N, Tang X, Yashar C. Intra- and interfraction movement of the cervix during radiation treatment in patients with cervical cancer. *Gynecol Oncol*, 112:2, 2009.

Eskander R, Warshak C, Ramos G, **Saenz CC**, Moore TR, Resnik R. The influence of gestational age on urgent delivery in patients with placenta accreta—Experience with 100 consecutive cases. *AJOG* 199:6 Supp A, 2009.

Eskander R, Warshak C, Ramos G, **Saenz CC**, Moore TR, Resnik R. Prenatal vs intraoperative diagnosis of placenta accreta: Effects on maternal outcomes in 100 consecutive cases. *AJOG* 199:6 Supp A, 2009.

Eskander R, Scanderberg D, **Saenz CC**, Yashar C. Comparison of CT and MRI cervical cancer brachytherapy target and normal tissue volumes. Oral Presentation, American Radiotherapy Annual Clinical Meeting, May 2009.

Eskander R, Grabowski J, Saenz N, **Saenz CC**. Management of 195 Benign and Malignant Ovarian Masses In a Pediatric Population: Evaluation of Operative Collaboration of Ovarian Preservation. Oral Presentation, Western Association of Gynecologic Oncologists Annual Meeting, June 2010.

Ward KK, **Saenz CC**, McHale MT, Alvarez EA, Plaxe SC. Changing Demographics of Cervical Cancer in the United States (1973-2007). Oral Poster Presentation, Society of Gynecologic Oncology Annual Meeting, March 2011.

Ballas J, Ramos GA, Warshak C, Hull A, **Saenz C**, Moore T, Resnik R. Preoperative uterine artery balloon catheters and surgical outcomes in pregnancies complicated by placenta accreta - a management paradox. Poster Presentation, Society of Maternal and Fetal Medicine Annual Meeting, February 2012.

Abbott Y, Shah N, Ward KK, McHale MT, Alvarez EA, **Saenz CC**, Plaxe SC. A program of social worker mediated introduction to psychosocial services improves patients' acceptance and access. *Gynecol Oncol*, 125:1, 2012.

Ward KK, Shah, NR, McHale MT, **Saenz CC**, Alvarez EA, Plaxe SC. Cardiac death is the most significant determinant of mortality for endometrial cancer patients and survivors. *Gynecol Oncol*, 125:1, 2012.

Korenaga T-RK, Ward KK, McHale MT, **Saenz CC**, Plaxe SC. Racial disparities in surgical procedure for localized endometrial cancer. Poster presentation American Society of Clinical Oncology Annual Clinical Meeting, June 2012.

Korenaga T-RK, Ward KK, McHale MT, **Saenz CC**, Plaxe SC. Place of residence modifies racial/ethnic disparities in the incidence of endometrial cancer. Poster presentation American Society of Clinical Oncology Annual Clinical Meeting, June 2012.

Shah N, Ward K, McHale M, Alvarez E, **Saenz C**, Plaxe S. Estimated rate of decline in radical hysterectomies available for training in the US, 1998–2008. *Gynecol Oncol*, 127:1, 2012.

Korenaga T-RK, Ward KK, McHale MT, **Saenz CC**, Plaxe SC. Regional variation in post-operative radiation therapy for early endometrial cancer. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2013.

Korenaga T-RK, Ward KK, McHale MT, **Saenz CC**, Plaxe SC. Regional variation in the incidence of gynecologic malignancies in the US. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2013.

Ward KK, Roncancio AM, Shah NR, Davis MA, **Saenz CC**, McHale MT, Plaxe SC. Creating a risk of readmission score for gynecologic oncology patients. Poster presentation, American Society of Clinical Oncology Annual Clinical Meeting, June 2013.

Shah NR, Ward KK, Davis M, Plaxe SC, **Saenz CC**, McHale MT. (2013, June) Robotic surgery for the treatment of uterine malignancy. Oral presentation, Western Association of Gynecologic Oncologists Annual Meeting, June 2013.

Shah NR, Ward KK, Davis M, Plaxe SC, **Saenz CC**, McHale MT. Urinary Diversions: A Time to Enrich Surgical Training? Oral Presentation, Western Association of Gynecologic Oncologists Annual Meeting, June 2013.

Davis M, Ward K, Shah N, **Saenz C**, McHale M, Plaxe S. After cytologic screening, what's next? Regional variation in cervical cancer prevention in the United States. Oral presentation, Western Association of Gynecologic Oncologists Annual Meeting, June 2013.

Shah NR, Ward KK, Davis M, Bean LM, **Saenz CC**, McHale MT, Plaxe SC. Trends in the use of minimally invasive surgery for the treatment of cervical cancer. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2014.

Bean LM, Ward KK, Shah NR, Davis MA, **Saenz CC**, Plaxe SC, McHale MT. Survival of women with microinvasive adenocarcinoma of the cervix is not improved by radical surgery. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2014.

Thung M, Mirsadraei L, **Saenz CC**, Datnow B. Invasive mixed endocervical and intestinal type adenocarcinoma of the uterine cervix in a

patient with Peutz-Jeghers Syndrome. Poster presentation, College of Anatomic Pathology Annual Meeting, September 2014.

Pettit KE, Sargent J, Ballas J, Warshak CR, Hull AD, Resnik R, **Saenz CC**, Ramos GA. Morbidities associated with antepartum bleeding in women with placenta accreta. Poster presentation, Society of Reproductive Investigation Annual Meeting, March 2015.

Pettit KE, Sargent J, Ballas J, Warshak CR, Hull AD, Resnik R, **Saenz CC**, Ramos GA. Comparison of morbidities associated with previa versus non-previa placentation in women with placenta accrete. Poster Presentation, Society of Reproductive Investigation Annual Meeting, March 2015.

Anderson K, Davis M, Shah NR, Bean L, **Saenz CC**, Plaxe SC, McHale MT. Beyond fertility: the safety of ovarian preservation in women with complex endometrial hyperplasia with atypia. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2015.

Davis MA, Ward KK, Shah NR, **Saenz CC**, McHale MT, Plaxe SC. Hospice utilization among gynecologic oncology patients is associated with payer and primary tumor site. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2015.

Bean LM, Workman PM, Shah NR, Davis MA, Kurnit KC, **Saenz CC**, McHale MT, Plaxe SC. National age standardized rate of ovarian cancer correlates with human development index; analysis of data from 165 countries. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2015.

Workman PM, Plaxe SC, Bean LM, **Saenz CC**, McHale MT. National age standardized rate of uterine corpus cancer correlates with human development Index;, analysis of data from 154 countries. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2015.

Kurnit KK, Ward KK, Bean LM, McHale MT, **Saenz CC**, Plaxe SC. Survivors of uterine malignancy have greater healthcare needs than the general population. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2015.

Taylor K, Bean LM, Anderson KM, Davis MT, McHale MT, **Saenz CC**, Plaxe SC. A population-based study of rare malignant trophoblastic neoplasms: Epithelioid trophoblastic tumor and placental site trophoblastic tumor. Poster presentation: Society of Gynecologic Oncology Annual Meeting, March 2016.

Puljic A, Plaxe SC, McHale MT, **Saenz CC**, Bean LM, Anderson KA, Taylor K. The role of preoperative radiation therapy in endometrial cancer. Poster presentation: Society of Gynecologic Oncology Annual Meeting, March 2016

Bean LM, Taylor K, Anderson KM, Davis MA, **Saenz CC**, Plaxe SC, McHale MT. Should ovarian preservation be considered for women younger than 60 years with endometrial carcinoma? Poster presentation: Society of Gynecologic Oncology Annual Meeting, March 2016.

Anderson KM, Hillman RT, Bean LM, Davis MA, **Saenz CC**, McHale MT, Plaxe SC. Effects of evolving treatment strategies on the incidence-based mortality of advanced ovarian cancer. Poster presentation: Society of Gynecologic Oncology Annual Meeting, March 2016.

Bean LM, Anderson KM, Taylor K, Davis MA, **Saenz CC**, McHale MT, Plaxe SC. Malignant Brenner tumor of the ovary: A population-based study. Poster presentation: Society of Gynecologic Oncology Annual Meeting, March 2016.

Hendrickson-Cahill W, Tierney NM, **Saenz CC**, McHale MT, Plaxe SC. A population-based study of malignant neuroendocrine tumors of the female genital tract. Poster presentation: Society of Gynecologic Oncology Annual Meeting, March 2016.

Anderson K, Davis MA, Bean L, **Saenz C**, Plaxe S, McHale M. Increasing incidence of primary fallopian tube cancer in association with scientific evidence for histologic reclassification. Oral presentation, Western Association of Gynecologic Oncologists Annual Meeting, June 2016.

Mell L, Sirak I, Wei L, Tarnawski R, Mahantshetty U, Yashar C, McHale M, Wright M, Pritz J, Straube W, Xu R, Kasaova L, Michalski J, Bosch W, Followill DS, Schwarz J, Honerkamp-Smith G, Lowenstein Leif J, **Saenz C**, Einck J, Koonings P, Harrison T, Khorprasert C, Shi M, Plaxe S, Mundt A. Phase II multi-center clinical trial of bone marrow-sparing intensity modulated radiation therapy with concurrent cisplatin for Stage IB-IVA cervical cancer. Oral Presentation, American Society for Radiation Oncology Annual Meeting, Sept 2016.

Mell LK, **Saenz CC**, Yashar CM, McHale MT, Einck JP, Wright ME, Noticewala SS, Xu R, Plaxe SC, Mundt AJ. Phase 1 trial of bone marrow sparing intensity modulated radiation therapy with concurrent cisplatin and gemcitabine in Stage IB-IVA cervical cancer. Int J of Radiation Oncol Biol Phys, 96:p.S14, 2016.

Shen JP, Bojorquez-Gomez A, Hunag J, Hofree M, Klepper K, Beckett A, **Saenz C**, Kreisberg J, Ideker T. A platinum-resistant subtype of high-grade serous ovarian cancer identified by a network of somatic mutations. Poster presentation: ASCO, Annual Meeting, June 2017.

BOOK CHAPTERS

Gurin CC and Mitchell MS. (1998). Principles of Immunology and Immunotherapy. In: Synopsis of Gynecologic Oncology, Fifth edition. Morrow CP, Curtin JP, Townsend DE, editors. Churchill Livingstone.

Saenz CC and Dowdy SF. (2005). Transmembrane Delivery of Protein and Peptide Drugs into Cancer Cells. In: Delivery of Protein and Peptide Drugs in Cancer, Torchilin V, editor. Imperial College Press.

PUBLICATIONS

Flamant F, **Gurin CC**, Sorge JA: An embryonic DNA-binding protein specific for the promoter of the retrovirus long terminal repeat. Molec Cell Biol 7:3548-3553, 1987. PMID: 2824991.

Gurin CC, Federici MG, Kang L, Boyd J: Causes and consequences of microsatellite instability in endometrial carcinoma. Cancer Research 59:462-466, 1999. PMID: 9927063.

Gemignani ML, Chi D, **Gurin CC**, Curtin JP, Barakat RR: Splenectomy in recurrent epithelial ovarian cancer. Gynecol Oncol 72:407-410, 1999. PMID: 10053114.

Hull AD, Salerno CC, **Saenz CC**, Pretorius DH: Three-dimensional ultrasonography and the diagnosis of placenta percreta with bladder involvement. J Ultrasound Med 18:853-856, 1999. PMID: 10591451.

Rock CL, Moskowitz A, Huizar B, **Saenz CC**, Clark JT, Daly TL, Chin H, Behling C, Ruffin MT 4th: High vegetable and fruit diet intervention in premenopausal women with cervical intraepithelial neoplasia. J Am Diet Assoc 101:1167-1174, 2001. PMID: 11678487.

Snyder EL, Meade BR, **Saenz CC**, Dowdy SF: Treatment of terminal peritoneal carcinomatosis by transducible p53 activating peptide. PLoS-Biology 2:186-193, 2004. PMID: 14966535.

Eitan R, **Saenz CC**, Venkatraman ES, Hann L, Bach, A, Gretz E, Barakat RR, Chi DS. Pilot study prospectively evaluating the utility of the measurement of preoperative sonographic endometrial thickness in patients with endometrial cancer. Menopause 12:27-30, 2005. PMID: 15668597.

Snyder EL*, **Saenz CC***, Denicourt C, Meade BR, Cui X, Kaplan IM, Dowdy SF. Selective targeting and killing of tumor cells expressing the CXCR4 receptor by transducible anti-cancer peptides. *Cancer Res.* 65:10646-50, 2005. [*Denotes Co-First Authors] PMID: 16322205.

Denicourt C., **Saenz CC**, Datnow B., Cui X., Dowdy S.F. Relocalized p27 Kip1 Tumor Suppressor. *Cancer Res.* 67: 9238-43, 2007. PMID: 17909030.

Warshak CR, Ramos GA, Eskander R, Benirschke K, **Saenz CC**, Kelly TF, Moore TR, Resnik R. Effect of predelivery diagnosis in 99 consecutive cases of placenta accreta. *Obstet Gynecol.* 115:65-9, 2010. PMID: 20027036.

Eskander R, Scanderberg D, **Saenz CC**, Yashar C. Comparison of computed tomography and magnetic resonance imaging in cervical cancer brachytherapy target and normal tissue volumes. *Int J. Gynecol Cancer* 20:47-53, 2010. PMID: 20130502.

Haripotepornkul NH, Nath SK, Scanderbeg D, **Saenz C**, Yashar CM. Evaluation of intra- and inter-fraction movement of the cervix during intensity modulated radiation therapy. *Radiother Oncol.* 98:347-51, 2011. PMID: 21216480.

Eskander, RN, Bristow, RE, Saenz NC, **Saenz CC**. A retrospective review of the effect of surgeon specialty on the management of 190 benign and malignant pediatric and adolescent adnexal masses. *J Pediatric Adolesc Gynecol.* 24:282-5, 2011. PMID: 21600810.

Ward KK, Shah NR, **Saenz CC**, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol.* 126:176-9, 2012. PMID: 22507532.

Ward KK, Shah NR, **Saenz CC**, McHale MT, Alvarez, EA, Plaxe SC. Changing demographics of cervical cancer in the United States (1973-2008). *Gynecol Oncol.* 126:330-3, 2012. PMID: 22668881.

Ballas J, Hull AD, **Saenz C**, Warshak CR, Roberts AC, Resnik RR, Moore TR, Ramos GA. Preoperative intravascular balloon catheters and surgical outcomes in pregnancies complicated by placenta accreta: a management paradox. *AJOG* 207:e1-5, 2012. PMID: 22831808.

Liang Y, Bydder M, Yashar CM, Rose BS, Cornell M, Hoh CK, Lawson JD, Einck J, **Saenz C**, Fanta P, Mundt AJ, Bydder GM, Mell LK. Prospective study of functional bone marrow-sparing intensity modulated radiotherapy with concurrent chemotherapy for pelvic malignancies. *Int J Radiat Oncol Biol Phys*, 85:406-14, 2013. PMID: 22687195.

Abbott Y, Shah NR, Ward KK, McHale MT, Alvarez EA, **Saenz CC**, Plaxe SC. Use of psychosocial services increases after a social worker-mediated intervention in gynecology oncology patients. *Health Soc Work*, 38:113-21, 2013. PMID: 23865288.

Kim JS, Ward KK, Shah NR, **Saenz CC**, McHale MT, Plaxe SC. Excess risk of *Clostridium difficile* infection in ovarian cancer is related to exposure to broad-spectrum antibiotics. *Support Care Cancer*, 21:3103-7, 2013. PMID: 23839499.

Ward KK, Roncancio AM, Shah NR, Davis MA, **Saenz CC**, McHale MT, Plaxe SC. The risk of uterine malignancy is linearly associated with body mass index in a cohort of US women. *Am J Obstet Gynecol*. 209:e1-5, 2013. PMID: 23938608.

Mell LK, Carmona R, Gulaya S, Lu T, Wu J, **Saenz CC**, Vaida F. Cause-specific effects of radiotherapy and lymphadenectomy in stage I-II endometrial cancer: a population-based study. *J Natl Cancer Inst*. 105:1656-66, 2013. PMID: 24123960.

Ward KK, Roncancio AM, Shah NR, Davis MA, **Saenz CC**, McHale MT, Plaxe SC. Bariatric surgery decreases the risk of uterine malignancy. *Gynecol Oncol*. 133:63-6, 2014. PMID: 24680593.

Hillman RT, Ward K, **Saenz C**, McHale M, Plaxe S. Barriers prevent access to personalized therapies identified by molecular tumor profiling of gynecologic malignancies. *J Pers Med*. 5:165-73, 2015. PMID: 26011384.

Shah NR, Ward KK, Davis, MA, McHale MT, **Saenz CC**, Plaxe SC. Decline in radical hysterectomies for early cervical cancer may affect gynecologic oncology training. *Am J Clin Exp Obstet Gynecol*, 2:65-71, 2015.

Barrett CL, DeBoever C, Jepsen K, **Saenz CC**, Carson DA, Frazer KA. Systematic transcriptome analysis reveals tumor-specific isoforms for ovarian cancer diagnosis and therapy. *Proc Natl Acad Sci*. 112:E3050-7, 2015. PMID: 26015570.

Simpson DR, Scanderbeg DJ, Carmona R, McMurtrie RM, Einck J, Mell LK, McHale MT, **Saenz CC**, Plaxe SC, Harrison T, Mundt AJ, Yashar CM. Clinical Outcomes of Computed Tomography-Based Volumetric Brachytherapy Planning for Cervical Cancer. *Int J Radiat Oncol Biol Phys*. 93:150-7, 2015. PMID: 26130230.

Kurnit KC, Ward KK, McHale MT, **Saenz CC**, Plaxe SC. Increased

prevalence of comorbid conditions in women with uterine cancer. *Gynecol Oncol.*13:731-4, 2015. PMID: 26160712.

Shah NR, Ward KK, Plaxe SC, **Saenz CC**, McHale MT. Urinary diversions: A time to enrich surgical training? *Gynecol Oncol.* 140:120-3, 2016. PMID: 26556767.

Vavinskaya V, Baumgertner JM, Ko A, **Saenz CC**, Valasek MS. Low-grade appendiceal mucinous neoplasm involving the endometrium and presenting with mucinous vaginal discharge. *Case Rep Obstet Gynecol.* 2016:6841989. PMID: 27843660.

Kurnit KC, Bean LM, Plaxe SC, **Saenz CC**, McHale MT. 2016. Squamous cell carcinoma of the vulva presenting as an isolated inguinal lymph node metastasis: A Case Report. *J Repro Med.* 61:612-614, 2016.

Tierney NM, **Saenz C**, McHale M, Ward K, Plaxe S. Industry Payments to Obstetrician-Gynecologists: An Analysis of 2014 Open Payments Data. *Obstet Gynecol.* 127:376-82, 2016. PMID: 26942368.

Noticewala SS, Li N, Williamson CW, Hoh CK, Shen H, McHale MT, **Saenz CC**, Einck J, Plaxe S, Vaida F, Yashar CM, Mell LK. Longitudinal changes in active bone marrow for cervical cancer patients treated with concurrent chemoradiotherapy. *Int J of Radiat Oncol Biol Phys,* 97:797-805, 2017. PMID: 28244416.

Taylor KN, McHale MT, **Saenz CC**, Plaxe SC. Diagnosis and treatment of *Clostridium difficile* colitis: Review of the literature and a perspective in gynecologic oncology. *Gynecol Oncol.* 144:428-37, 2017. PMID: 27876339.

Hillman RT, **Saenz CC**, McHale MT, Plaxe SC. Fertility preservation and survival among young women with early ovarian cancer living in US counties with gynecologic oncologist services. *Int J Gynaecol Obstet.* 137:157-63, 2017. PMID: 28170079.

Mell LK, Sirák I, Wei L, Tarnawski R, Mahantshetty U, Yashar CM, McHale MT, Xu R, Honerkamp-Smith G, Carmona R, Wright M, Williamson CW, Kasaová L, Li N, Kry S, Michalski J, Bosch W, Straube W, Schwarz J, Lowenstein J, Jiang SB, **Saenz CC**, Plaxe S, Einck J, Khorprasert C, Koonings P, Harrison T, Shi M, Mundt AJ; INTERTECC Study Group. Bone marrow-sparing intensity modulated radiation therapy with concurrent cisplatin for Stage IB-IVA cervical cancer: An international multicenter Phase II clinical trial (INTERTECC-2). *Int J of Radiation Oncol Biol Phys.* 97:536-45, 2017. PMID: 28126303.

Delaney JR, Patel CB, Willis KM, Haghighiabyaneh M, Axelrod J, Tancione I, Lu D, Bapat J, Young S, Cadassou O, Bartakova A, Sheth P, Haft C, Hui S, **Saenz C**, Schlaepfer DD, Harismendy O, Stupack DG. Haploinsufficiency networks identify targetable patterns of allelic deficiency in low mutation ovarian cancer. *Nat Commun.* 8:14423, 2017. PMID: 28198375.

Mirsadraei L, Hodkoff A, Jones K, Shabaik A, Kader K, **Saenz CC**, Monitironi R, Tacha, DE, Fadare O, Hansel DE. Serous carcinoma mimicking primary urothelial carcinoma on clinical evaluation and pathology: A potential diagnostic pitfall. *Arch Pathol Lab Med.* 142:168-77, 2018. PMID: 28795841.

EXHIBIT B

List of Testimony Given in the Last Four Years
Cheryl Christine Saenz, M.D.

Depositions

2017

Echeverria v. Johnson & Johnson, No. BC628228 (Cal. Super. Ct. L.A. Cnty.)

Dimberg v. Wagner, No. CICDS1309968 (Cal. Super Ct. San Bernardino Cnty.)

DaCosta v. Valleycare Medical Foundation, No. RG15762040 (Cal. Super Ct. Alameda Cnty.)

2018

Ingham v. Johnson & Johnson, No. 1522-CC10417-01 (Mo. Cir. Ct.) (deposed twice)

Flanagan v. Strohmeyer, No. 37-2016-00007369-CU-MM-NC (Cal. Super. Ct. San Diego Cnty.)

Brower v. Johnson & Johnson, No. 16-EV-005534-E (Ga. Fulton Cnty.)

Forrest v. Johnson & Johnson, No. 1522-CC00419-01 (Mo. Cir. Ct.)

2019

Flanagan v. Strohmeyer, No. 37-2016-00007369-CU-MM-NC (Cal. Super. Ct. San Diego Cnty.)

Trial Testimony

2017

Echeverria v. Johnson & Johnson, No. BC628228 (Cal. Super. Ct. L.A. Cnty.)

2018

Dimberg v. Robert Wagner, No. CICDS1309968 (Cal. Super Ct. San Bernardino Cnty.)

Ingham v. Johnson & Johnson, No. 1522-CC10417-01 (Mo. Cir. Ct.)

Flanagan v. Strohmeyer, No. 37-2016-00007369-CU-MM-NC (Cal. Super. Ct. San Diego Cnty.)

2019

Flanagan v. Strohmeyer, No. 37-2016-00007369-CU-MM-NC (Cal. Super. Ct. San Diego Cnty.)